THE ACUTE EFFECT OF TOBACCO-SMOKING AND NICOTINE ON THE ELECTROCARDIOGRAM

ESPECIALLY DURING INDUCED HYPOXIA

A CLINICAL AND EXPERIMENTAL INVESTIGATION

BY

BERTIL VON AHN

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BY

BERTIL VON AHN
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Preface

This investigation was initiated in the spring of 1951, and was carried out at the Medical Clinic of the Academic Hospital, Uppsala. My chief, Professor Erik Ask-Upmark, has encouraged me in my work and kindly placed necessary apparatus at my disposal. I have had the great privilege of working at his clinic for some years, and I wish to express my very deep gratitude to him.

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Uppsala, April 1954.

Bertil von Ahn

Introduction

It has long been considered that tobacco-smoking may cause or aggravate cardiovascular disease. It has been assumed that tobacco produces its deleterious effects on the heart chiefly in two ways: firstly by precipitating coronary spasm and angina pectoris; and secondly by predisposing to arteriosclerosis, especially coronary sclerosis. There are still divided opinions as to the supposed injurious influence of tobacco on the heart. The great increase in the consumption of cigarettes during the last two or three decades has been associated with a simultaneous increase in the incidence of diseases of the heart, stomach, and lungs (bronchial carcinoma). Thus the tobacco problem is of great social importance. Our knowledge of it is still limited, in spite of an enormous literature. The problem has been discussed on an inadequate basis of fact, which explains the many greatly conflicting opinions.

This study is an attempt to ascertain new facts on the immediate effects of tobacco on the heart.

CHAPTER I

Tobacco-Smoking and the Cardiovascular System

A Brief Review of the Literature

A short review of the literature follows to give an idea of the general aspects of the problem, since the electrocardiogram can only be properly assessed against the clinical background.

Graves (1848) found disturbances of heart-action in connection with heavy smoking, and was the first to publish observations on this question. In 1862 Beau claimed that tobacco-smoking could provoke angina pectoris under certain conditions including excessive use of tobacco, particular individual susceptibility, and debilitating factors.

Favarger (1887) was of the opinion that nicotine was the most important of the poisons in tobacco-smoke. He described chronic tobacco poisoning in detail, and brought up the question of whether the disturbances of cardiac efficiency provoked by excessive use of tobacco are only functional, or whether pathological changes may also be produced. According to him the use of nicotine leads to functional constriction of the coronary arteries (coronary spasm) which when repeated over many years results in inadequate blood supply to the heart muscle, with 'fatty degeneration' of the heart as a consequence. In a later publication (1914) he develops this idea, and describes several cases of fatal chronic heart disease in heavy smokers. Chronic tobacco poisoning is given as the true cause of this heart disease. On the other hand, he found persons aged 70—80 years without any evidence of chronic tobacco poisoning, in spite of heavy smoking over many years.

Huchard gave in his textbook on medicine (1899) a detailed account of chronic nicotine poisoning, together with a description of several cases in which excessive use of tobacco had provoked pains of anginal type. He introduced the term 'tobacco angina' ('l'angine de poitrine tabagique'), describing this syndrome in detail. He distinguished between the different types of tobacco angina. (1) Functional angina, ('l'angine spasmo-tabagique'), due to coronary spasm, which quickly subsides after rejection of tobacco. (2) Organic, severe angina due to nicotine sclerosis, ('l'angine sclero-tabagique'). (3) Benign, pseudo-angina, ('l'angine gastro-tabagique'), caused by dyspeptic disturbance secondary to tobacco abuse.

Willson (1915) maintained that tobacco has an insidious influence on the arteries. He believed it to be the chief cause of arteriosclerosis not due to syphilis or old age. His opinion was, however, chiefly based on von Otto's experiments on rabbits (see below). The findings of these experiments are applied to man without reservation. He proclaimed: 'Tobacco destroys the best we have!'

In Kraus-Brugsch's Textbook on Diseases of the Heart (1925) Plesch describes in detail the effect of tobacco on the cardiovascular system. He discusses very critically the opinions of Favarger and others on the alleged deleterious influence of tobacco on the heart. According to Plesch, chronic excessive use of tobacco does not harm the heart and vessels. Tobacco may, however, via the nervous system provoke disturbances of function and sensation.

Külbs (1924) gives a detailed account of the symptomatology of tobacco abuse. According to this author, disabilities, chiefly cardiac neuroses with extrasystoles, palpitations (especially at night), and permanent bradycardia, occur in smokers between the ages of 20 and 40 years. After the age of 50 angina pectoris develops as a sequel to excessive tobacco use. He concludes that heavy smoking predisposes to arteriosclerosis.

Plenge (1930) describes two heavy smokers, aged 46 and 40 years respectively, who died of heart disease. Coronary sclerosis and heart infarction were revealed by autopsy in both cases. The other arteries were almost normal. Tobacco was regarded to have been the most probable cause of the atheromatosis, bearing in mind the supposed special affinity of tobacco for the coronary arteries (Pawinski). Both the history and the cause of the disease indicate unconditionally that the excessive consumption of tobacco was an aetiological factor in these cases, according to Plenge.

Schönberg (1935) reports five cases of sudden death in heavy cigarette smokers. Coronary disease was found in all of the cases at autopsy. He attributes the heart disease and the sudden death to chronic abuse of nicotine.

According to Leschke (1935) the harmful influence of nicotine on the vessels has been much overestimated. Tobacco may, however, exert an injurious effect on persons predisposed to arteriosclerosis, and especially to angina pectoris. He emphasizes the fact that arteriosclerosis is a rare disease in South America, where the consumption of tobacco is very high. It may be mentioned in this connection that tobacco labourers do not suffer from arteriosclerosis any more than other persons (Brugsch, 1936).

Strauss (1937), in an extensive survey, has given an account of the influence of nicotine on the heart and vessels and on the electrocardiogram. He gives a great number of references, and concludes, that chronic nicotine abuse exerts a deleterious effect on the heart and vessels, almost selectively

affecting the coronary arteries. Smoking produces coronary spasm and precipitates angina pectoris.

Master, Dack, and Jaffe (1937) maintain, contrary to most authors, that smoking has no influence on the incidence of coronary thrombosis.

Deneke (1936), Assmann (1939), Hassencamp (1939), Reichel (1939), Högler (1941), and Laurentius (1941) also stress the injurious effect of tobacco on the heart and blood vessels. According to these authors the use of tobacco produces coronary spasm and predisposes to arteriosclerosis. Insidious organic lesions are provoked by the long-continued use of tobacco (Hassencamp). Weicker (1939) describes eight cases of heart infarction, the patients ranging in age from 35 to 53 years, which he ascribes to excessive use of nicotine. Büchner (1939) is of the opinion that nicotine, acting via the vagus, produces constriction of the coronary vessels. Pains of anginal type occur in young persons as a result of tobacco abuse. These pains subside when smoking is stopped. According to his view continuous stimulation of the vagus, causing a chronic constriction of the coronary vessels, is involved in these cases. Lickint (1939) has in his encyclopaedic work 'Tabak und Organismus' collected an enormous number of references up to the year 1939. He too emphasizes the harmful effect of tobacco on the cardiovascular system. Like most authorities, he states that tobacco produces coronary spasm and predisposes to arteriosclerosis. He has seen autopsies on heavy smokers in whom the coronary arteries were found to be extremely sclerotic. Other arteries appeared to be conspicuously intact. According to Lickint, nicotine thus has a selective affinity for the coronary arteries, which would appear to constitute a 'locus minoris resistentiae' to this drug.

Much statistical evidence has been published in attempts to illustrate the relation of tobacco-smoking to coronary disease.

In 1914 Pawinski published a series of 1,075 cases of coronary sclerosis and angina pectoris in males, 457 of whom (41.9%) were heavy smokers. According to him arteriosclerosis is caused chiefly by obesity, the second most important factor being tobacco abuse. He ascribed 19.4% of the cases to tobacco abuse alone, and 41.9% to tobacco in combination with other factors. He considered tobacco to have a special affinity to the coronary arteries, and heavy smoking to be very harmful to heart and blood vessels. No post mortem material, however, is described, and the diagnosis of coronary sclerosis seems to have been based on clinical evidence only.

Johnson (1929) has described a series of 60 fatal cases of angina pectoris, all men, of whom 42 (70%) were smokers and 18 (30%) non-smokers. The average age of death was for smokers 61.3 years, and for non-smokers 62.5 years. Since 70% of the patients were smokers, tobacco may be suspected to have played a part in the aetiology of the disease process. In a control series of 1,000 men, their names picked at random from telephone directories,

81.8% were smokers. According to Johnson, tobacco does not seem to play the important role in the aetiology of angina pectoris to which it has been ascribed.

White and Sharber (1934) have published a statistical study on the possible relation of tobacco to angina pectoris. 750 patients with angina pectoris, and as many persons without, were questioned as to their previous smoking habits. Both groups were equivalent as to sex, age, and conditions of life. Of the patients with angina pectoris 46.1% were non-smokers and 24.4% heavy smokers; of the control group 37.2% were non-smokers and 33.5% heavy smokers. According to the authors neither tobacco use nor abstinence from it plays any important role in the aetiology of angina pectoris.

English, Willius, and Berkson (1940) published statistics with conflicting results. The series consisted of 1,000 patients of 40 years or more, with angina pectoris, and was subdivided into smokers and non-smokers; and 1,000 patients without heart disease, subdivided in the same way into smokers and non-smokers. Of the patients with angina pectoris 69.8% were smokers, 66.3% of the other series being smokers. The difference is not statistically significant. In the age group 40—59 years the incidence of coronary disease among smokers was three times that among non-smokers. Smoking at an early age is considered to predispose to coronary disease. In a special table the authors attempt to illustrate the degree of smoking to the incidence of heart disease. The table is composed of 208 smokers and as many non-smokers in the age group 40—49 years. Excessive smokers (only 34 cases) showed the greatest incidence of heart disease (5.9% compared to 1% in non-smokers).

Glendy, Levine, and White (1937) have compared 100 patients under 40 years of age and suffering from coronary disease with 300 persons aged 80 years and over, with regard to several factors including their tobacco habits. In the older age group 55.8% were smokers and 44.2% non-smokers; in the younger group 93.3% were smokers and 6.7% non-smokers. Thus an apparent difference in tobacco habits existed between the two groups.

Pearl (1938) published a statistical study of longevity among smokers in relation to that among non-smokers. The series consisted of 6,813 men, of whom 2,094 were non-smokers, 2,814 moderate smokers, and 1,905 heavy smokers. The moderate smokers showed a slightly raised death-rate, whereas in the heavy smokers the death-rate was considerably raised (between 30 and 50 years nearly 100%).

According to Bergstrand (1939) there is no statistical proof that coronary sclerosis and secondary heart infarction are produced by tobacco abuse.

Hove (1950) found, in connection with cardiac examination of 1,723 individuals aged 26 –28, that two thirds were smokers. 542 of the examined

cases showed evidence of organic or functional heart disease. The patients with organic heart disease actually consumed less tobacco than the average, and those with functional disorders smoked little more than the average. Patients with neuroses, hypertension, and isolated electrocardiographic anomalies showed greater tobacco use than the average.

Hochrein (1941—43) mentions that nicotine abuse often appears in the history of patients with heart infarction. According to his view, nicotine causes coronary constriction and may be a contributory factor in the aetiology of heart infarction. White (1945) is of the opinion that tobacco causes no actual heart disease, but may in susceptible individuals or on abuse, produce tachycardia and arrhythmias. According to Friedberg (1949), there is no significant evidence that excessive tobacco use should predispose to disease of the coronary arteries or acute coronary occlusion. Roth (1951) states that smoking is most likely a contributory factor and not the primary cause of cardiovascular disease.

Many investigators have tried to produce arteriosclerosis in animals by means of nicotine, the rabbit being the experimental animal most commonly employed (Boveri, 1905; Baylac, 1906; Gouget, 1906; Adler and Hensel, 1906; Lesieur, 1907; Zebrowski, 1907; Lee, 1908; von Otto, 1911; Schmiedl, 1913; Romm and Kuschnir, 1928;). These experiments have usually led to the production of aortic lesions in the form of necrosis and calcification in the media. The changes in the media have been of the type found in the media of the arteries of the extremities in man, as described by Mönckeberg (1903). Adler and Hensel and von Otto also succeeded in producing considerable thickening of the intima. It has been much discussed whether any conclusions on the relationship of nicotine to arteriosclerosis in man may be drawn from these experiments on rabbits. Schmiedl points out that the change in the media obtained in rabbits ('arterionecrosis') is not identical with the arteriosclerosis of the intima found in man. As to these experiments on rabbits it may be observed that the series have been too small, and that few or no control experiments have been done. It must also be recalled that similar changes in the vessels can develop spontaneously in the rabbit (Schmiedl; Romm and Kuschnir; Thienes and Butt; Bragdon) or under the influence of many widely-differing poisons (Schmiedl; Staemmler).

Since the rabbit is considered to have a particularly susceptible arterial system (Lee), it is of great interest to observe how other experiment animals, for instance the rat and dog, react to nicotine. Staemmler (1935) was unable to produce any changes in the vessels in experiments on the rat, the coronary arteries in particular being examined. Thienes and Butt (1938), who also used rats, arrived at similar results, and conclude that smoking probably does not produce organic heart disease. Erbacher, Gumbrecht, and Loeser (1940) observed necrosis in the myocardium in experimental rats, whereas control animals showed no such changes. Hueper (1943) treated rats during 8—10 months with subcutaneous injections of nicotine, and succeeded in producing degenerative changes in arteries and arterioles.

Experiments on dogs have been done by Adler (1914) and Hueper (1943). Adler treated a dog with nicotine intravenously during seven months; no changes were observed in the arteries. Hueper, however, found the same changes in the arteries as in his experiments on rats, and he therefore concluded that nicotine has an arteriosclerogenic effect. It must be observed that he had no control series, a matter of some importance since arteriosclerosis can develop spontaneously both in dogs (Lindsay, Chaikoff, and Gilmore) and rabbits.

Summary

According to most authors tobacco-smoking produces coronary spasm and angina pectoris, and predisposes to arteriosclerosis and secondary heart infarction. In the past nicotine has been considered to have a special affinity for the coronary arteries, which are particularly liable to be affected by arteriosclerosis. The statistics which have been published concerning the possible relationship of tobacco to coronary disease are contradictory, and do not justify conclusions in any direction. The same can be said of the attempts which have been made to produce experimental nicotine arteriosclerosis in animals. In most of these experiments no adequate controls have been done and possible spontaneous sclerosis in the experimental animals has rarely been considered. The results of these experiments are thus of doubtful value, and cannot without reservation be applied to man.

In the following work the acute effects only of tobacco-smoking upon cardiac activity and the electrocardiogram will be discussed.

CHAPTER II

The Pharmacology of Smoking

Smoking as a Physical Process

Smoking is a process of dry distillation during which the nicotine is partially destroyed at the burning tip of the cigarette or cigar. Part of the nicotine is vaporized, some of the vapour being condensed in the cooler, proximal part of the cigarette. There is thus a concentration of nicotine in the butt, especially in the case of cigars. A cigar contains 17 mg. of nicotine per gram but the discarded butt contains 21—25 mg. of nicotine per gram (Lehmann, 1908). The smoke inhaled through a cigarette, for instance, is called the main stream, and that rising from the burning tip between puffs is called the side stream (Lehmann). The nicotine-concentration in cigarettes is about 2%, an ordinary cigarette weighing 1 g. thus containing 20 mg. of nicotine. During smoking 25—30% of the nicotine in a cigarette is destroyed by combustion, 30% passes into the main stream, 40% into the side stream, and 2—5% remains in the butt. In the case of cigars 10—15% of the nicotine goes into the main stream, 25—40% into the side stream, 50% is destroyed, and 5—10% remains in the butt (Preiss).

The Composition of Tobacco-smoke

The chemical composition of smoke has been analysed by Lehmann (1908), Lee (1908), and Wenusch (1939). It is composed of a gaseous fraction and a solid-fluid fraction (Wenusch). The former contains carbon monoxide, carbon dioxide, nitrogen, oxygen, hydrogen sulphide, hydrogen cyanide, and ammonia. The latter part consists chiefly of nicotine. Small quantities of a large number of other substances, including pyridine bases (collidine, lutidine), methyl alcohol, and organic acids, etc. are also present. For further details of the chemistry of tobacco-smoke, see Lickint (1939) and Wenusch.

Nicotine is considered to be the most important constituent of the smoke, with carbon monoxide next in importance (von Euler, 1931; Lickint). No special significance has been attached to the remaining constituents of the

smoke, except for the tar-like products (? carcinogenic factors). When it comes to the immediate effects of tobacco-smoke, it is thus chiefly nicotine and carbon monoxide which have to be considered.

Absorption of Nicotine and Carbon Monoxide in Smoking

Nicotine

In every puff about 40—50 ml. of smoke enters the mouth (Wenusch). On deep inhalation 88—92% of the nicotine is absorbed (Lehmann, 1908; Baumberger, 1923; Pierce, 1941). Various claims have been made as to the absolute amount of nicotine absorbed into the blood stream in the smoking of a cigarette. Lehmann gives 1.4—1.7 mg. according to one method, and 0.8—1.5 mg. according to another, Pierce gives 2.2—3.5 mg., Haag and Larson (1944) 3 mg., and Ling and Parry (1949) 0.4 mg. or less. On smoking a cigar 3.5—6.8 mg. is absorbed per gram cigar, according to one method, 1.7—2.5 mg. according to another (Lehmann). According to Storm van Leeuwen (1919) 2.5—4.25 mg. of nicotine per gram cigar are transferred into the main stream. Supposing that 90% of the nicotine in the main stream is absorbed, it would mean that 2.25—3.81 mg. of nicotine per gram cigar is taken into the body.

Carbon Monoxide

According to Baumberger (1923) about 8.3 ml. CO is produced by the smoking of one cigarette; according to Ehrishmann and Abel (1934) the figure is 17.25 ml. Wenusch (1939) found 20—40 ml. of carbon monoxide in the main stream on combustion of one gram of cigarette tobacco (= one cigarette). The corresponding value for one gram of cigar tobacco was 45—110 ml. of carbon monoxide. Thus cigar smoke contains considerably more carbon monoxide than cigarette smoke. Probably only slight quantities of carbon monoxide are absorbed on smoking without inhalation (Wenusch); but deep inhalation results in considerable quantities being taken up — according to Baumberger 61% of the content of carbon monoxide.

The carboxyhaemoglobin content of the blood in non-smokers has been given variously as 0.4% (Wennesland, 1945) and 1.0—1.5% (Gettler and Mattice, 1933). Noro and Saksela (1946) report a morning value of 0.34—0.28% of COHb in drivers and cleaners in the motor trade. Smokers consuming 10—20 cigarettes per day can have morning values of over 5% of COHb. In smokers the COHb-content increases considerably during the day

in connection with smoking: values from 2.5 –5.0% (Hanson and Hastings, 1933: Rühl and Lin, 1936) up to 10% of COHb (Wennesland; Noro and Saksela) have been reported, figures which are remarkably high.

The values to which the COHb-content of the blood can rise during or immediately after smoking are of great interest in this connection. Rühl and Lin found an increase in the COHb-content to 5 –10% (1 –2 volumes per cent), on the smoking of one or two cigarettes. Noro and Saksela found in one case 4.3% after the smoking of one cigarette and 9.2% after two cigarettes: and in another case 7% of COHb after the smoking of four cigarettes. The initial values in these two cases were 1.5% and 0.5% of COHb respectively.

It has also been discussed whether burning of the cigarette paper might produce any appreciable quantity of carbon monoxide. According to Wenusch and Schöller (1938) the paper of an ordinary cigarette weighs 0.04 gram, and a maximum of 1 ml. of carbon monoxide passes into the main stream from this.

In summary it can be said that considerable quantities of carbon monoxide may be absorbed by continuous smoking with inhalation.

The Fate of Nicotine in the Body

Pierce estimates that 71.4 mg. of nicotine is absorbed on the smoking of 20 cigarettes with deep inhalation. This exceeds the lethal dose, estimated to be 40—60 mg. (Lickint, 1939; Sollman, 1949). If this amount were retained in the blood stream, the concentration of nicotine would exceed 14 mg. per litre of blood. Wolf, Hawkins, and Giles (1948) have elaborated a sensitive method of spectrophotometric estimation of nicotine in the blood. By this method, which must be performed by a specialist, quantities as small as 1—50 gamma of nicotine in 10—20 ml. of blood can be determined. Wolf et al. (1948—49) arrived at the interesting result that after the smoking of 20 cigarettes in seven hours the content of nicotine in the blood showed an average increase of only 0.14 mg./litre of blood in 20 subjects. Hence their opinion that 80 –95% of the nicotine absorbed during smoking is metabolized during the period of smoking. Haag and Larson (1944) found that only 10% of the absorbed nicotine is excreted unchanged in the urine, and that excretion is complete in 16 hours has been shown by Finnegan, Larson, and Haag (1947). The remainder (90%) is relatively quickly metabolized and eliminated. It appears, however, as if the capacity for breaking down nicotine decreases with increasing age (Burn, 1951). According to Werle (1938) the detoxication of nicotine is completed in the lungs and, more particularly, in the liver by means of an enzyme.

The Influence of Nicotine on the Cardiovascular System

The immediate effect of tobacco-smoke is considered to be practically identical with that of nicotine (Sollman, 1949). The possibility cannot be precluded that the amount of carbon monoxide absorbed by the smoking of, say, one cigarette may be of toxicological importance. The most characteristic quality of nicotine is its influence on the autonomic ganglia, both sympathetic and parasympathetic, which, after a short period of stimulation, become partially blocked or paralysed (Langley and Dickinson, 1890). The effect on the cardiovascular system is very complex. The heart rate may be increased by stimulation of the sympathetic ganglia, or by blocking of the parasympathetic; or bradycardia may result from paralysis of the sympathetic ganglia, or from stimulation of the parasympathetic (Goodman and Gilman, 1941). The effect of nicotine depends on the size of the dose. In animal experiments nicotine causes primary bradycardia by vagal stimulation and secondary tachycardia by vagal paralysis (Meyer, 1912; Hett, 1920; Dickson, 1924). Vagal stimulation and coronary constriction are effects which are particularly emphasized (Hett; Romm and Kuschnir; von Euler). Tachycardia, rise in blood pressure, and vasoconstriction in the skin are provoked by the smoking of one cigarette, when small amounts of nicotine are absorbed. All these three phenomena are explained by nicotine stimulation of the sympathetic ganglia (Burn et al., 1945). According to Hoskins and Ranson (1915), the pressor effect of nicotine is to 50% dependent on a stimulation of the vasoconstrictor center, and to 50% on stimulation of the sympathetic ganglia. Nicotine also stimulates the suprarenals to increased liberation of adrenaline, and may also in this way raise the blood pressure (Cannon, Aub, and Binger, 1912; Stewart and Rogoff, 1919; Eichholtz 1923; Tainter, 1926; Kosdoba, 1930; Kobro, 1936; van Slyke and Larson, 1950). It has been discussed whether the quantity of nicotine absorbed in smoking could cause any appreciable increase in the secretion of adrenaline. Smoking as an adrenaline-stimulating factor is, according to Straub and Amann (1940), without practical importance. Cannon et al. state that in the cat 0.0035—0.0075 g. of nicotine leads to increased secretion of adrenaline. According to van Slyke and Larson, small doses of nicotine (0.01—0.04 mg./kg.) liberate adrenaline from the suprarenal glands of dogs.

Nicotine and the Coronary Circulation

Animal Experiments

Opinions have long been divided as to the influence of nicotine on the coronary circulation. This question is of great importance to the clinician. The immediate effect of smoking on the coronary circulation cannot, for

obvious reasons, be studied directly in man, but many animal experiments have been done which cast light on this question.

Meyer (1912) showed in experiments on curarized dogs, with the aid of artificial respiration, that nicotine had a constrictive effect on the coronary vessels. The dose of nicotine injected was 10 mg. Morawitz and Zahn (1914) arrived at the same result in experiments on cats. They used a dose as large as 5 mg. or more. Romm and Kuschnir (1928) found that nicotine produced considerable constriction of the coronary vessels and reduction of the coronary flow in normal rabbits — on an average 49%. Rabbits treated with nicotine over a long period reacted to this agent with considerably diminished coronary constriction and a reduction in the coronary flow by an average of 24%; according to the authors, this indicates considerable damage to the vasoconstrictor system. Mansfeld and Hecht (1933) examined the effect of tobacco-smoke and pure nicotine on Starling's heart-lung preparations from dogs. They noted considerable dilatation of the coronary vessels, the coronary circulation increasing to seven times the initial value. The effect was the same on an innervated heart-lung preparation. Laubry, Walser, and Deglaude (1933) studied the effect of nicotine on the coronary circulation in isolated rabbit hearts. They employed nicotine solutions in concentrations varying between 1:1,250,000 and 1:25,000. Small doses produced an increase of 30—60% in the coronary circulation, and moderate doses an increase of 5—20%; large doses, on the other hand, caused a decrease of 10—20%.

Dietrich and Schimert (1939) examined the influence of nicotine on the coronary flow in dogs under chloralose anaesthesia, by means of Rein's 'thermostromuhr'. They administered nicotine either in the form of cigarette-smoke or intravenously as pure nicotine in doses varying from 0.02—0.1 mg. up to 25 mg. In all the experimental animals they observed increased coronary flow. In 10 of the 19 dogs they noted in addition a decrease in coronary flow either at the beginning or at the end of the experiment. The decrease in the coronary circulation could in all cases be neutralized by atropine and accentuated by prostigmine.

The animal experiments referred to have given conflicting results, and have not definitively solved the problem of the influence of nicotine on the coronary circulation. The doses employed by Morawitz and Zahn in cats (5 mg. or more — about 2.5 mg. of nicotine per kg.) exceed considerably the amount absorbed by man during smoking. The 0.5 to 1 mg. nicotine which may be supposed to be absorbed on smoking one cigarette amounts to no more than 0.007—0.0143 mg. of nicotine per kg. in a 70 kg. man.

Burn, Truelove, and Burn published in 1945 a very interesting study giving a quite new angle on the problem of nicotine and the coronary circulation. Their experiment was based on the observation that acetylcholine liberates the antidiuretic hormone from the posterior lobe of the pituitary (Pickford,

1939). Burn et al. found that nicotine, too, has an antidiuretic effect in the rat. They also observed that the smoking of one or two cigarettes had an antidiuretic effect lasting 1—3 hours in man; an intravenous injection of 0.33 -1 mg. of nicotine (free base) had a similar antidiuretic effect. According to them, nicotine absorbed from cigarette-smoke probably stimulates the posterior lobe of the pituitary, with resulting liberation of antidiuretic hormone. Walker (1949) has shown that both smoking and injection of nicotine are accompanied by increased excretion of chlorides in the urine. This is a characteristic of posterior pituitary hormone. The smoking of one or two cigarettes had in this respect the same effect as the intravenous injection of 50 milliunits (mU) of posterior pituitary extract. Two distinct hormones are secreted by this gland, oxytocin and vasopressin. The effect of vasopressin (pitressin) is partly vasoconstrictory (Morawitz and Zahn, 1914; Rössler, 1930) and partly antidiuretic. It is still unknown whether two separate hormones or a single hormone with two active principles are concerned. According to Bülbring, Burn, and Walker (1949), it is considered that the antidiuretic hormone is identical with the vasoconstrictor hormone. They have shown in anaesthetized dogs that nicotine produces an initial dilatation of the coronary vessels, followed by secondary, prolonged vasoconstriction. The amount of nicotine required in order to reduce the coronary flow was, however, large. They consider this probably due to the fact that the anaesthetic diminished the response of the pituitary to nicotine. They found in addition, using heart-lung preparations from dogs, that injection of 5—50 mU of posterior lobe extract reduced the coronary flow by 5—25% during 30 minutes. Taylor and Walker (1951) have demonstrated an antidiuretic substance in human urine after the smoking of one cigarette; this they believe is probably identical with the antidiuretic hormone from the posterior pituitary. According to Burn and Grewal (1951) 3—190 mU of posterior lobe hormone is excreted in the urine after the smoking of one or two cigarettes. Burn (1951) therefore concludes that smoking may produce coronary constriction also in man.

These observations indeed bring new and interesting views on the tobacco problem, for the pharmacologist as well as for the clinician.

Nicotine and the Peripheral Circulation

Although the effect of nicotine on the coronary circulation cannot be determined directly in man, the peripheral circulation is readily available for observation. Examination can be done with the aid of the plethysmograph or by registration of the skin temperature. Peripheral vasoconstriction following smoking has been recorded plethysmographically by Bruce, Miller, and Hooker (1909); Lampson (1935); Abramson, Zazeela, and Oppenheimer

(1939); and Mulinos and Shulman (1940). Lampson found that the smoking of one cigarette with inhalation of the smoke produced sudden and pronounced peripheral vasoconstriction in a hand, lasting one hour; if there was no inhalation of the smoke the effect only continued for 15 minutes. According to Abramson et al. the peripheral vasoconstriction induced by smoking is limited to the vessels of the skin. They found no reduction of the blood flow in the forearm, whereas considerable decrease was noted in the hand. They consider this to be due to the fact that 85% of the tissues of the forearm consists of muscle, the vessels of which do not react to tobacco. In contrast, 50% of the tissues of the hand is made up of skin and subcutaneous tissue, in which the vessels react to nicotine with pronounced vasoconstriction. Mulinos and Shulman have shown that deep breathing alone can produce peripheral vasoconstriction which cannot be distinguished from that caused by smoking. Jarlov (1950) has, by means of photoelectric sphygmography, confirmed the vasoconstrictor effect of cigarette-smoke on the peripheral vessels in the fingers.

Fall in skin temperature at the extremities after smoking has been reported by Barker (1933), Maddock and Coller (1933), Wright and Moffat (1934), Moyer and Maddock (1940), Weatherby (1942), Evans and Stewart (1943), and Roth, McDonald, and Sheard (1944). Most investigators have agreed that nicotine is the constituent of the smoke which is responsible for the peripheral vasoconstriction. This has, however, been questioned by Evans and Stewart, who found a fall in skin temperature on smoking fully denicotinized cigarettes as well. According to these authors, the changes were due to sympathetic stimulation following irritation of the respiratory tract by the smoke. Roth et al. found that corn-silk cigarettes had no significant effect on the skin temperature; but the smoking of ordinary cigarettes caused an average fall of 1.8° C. in the skin temperature of the toes, and 3.2° C. in that of the fingers. Intravenous injection of 2 mg. of nicotine produced a quicker and more pronounced fall in skin temperature than did smoking. Maddock and Coller have shown that smoking caused no fall in the skin temperature of the toes after blocking the posterior tibial nerve with 2% procaine. They therefore considered it unlikely that nicotine has a direct effect on the vessels. They explained the peripheral vasoconstriction by stimulation of sympathetic ganglia. Rapaport, Frank, and Massell (1950) arrived at the same result. They found that smoking had no effect on the skin temperature and blood flow in a sympathectomized limb. They therefore came to the conclusion that the peripheral vasoconstriction is brought about by a nervous mechanism via the sympathetic fibres, and not by humoral factors such as adrenaline or posterior pituitary hormone.

Estimation of the peripheral circulation in the extremities by registration of the skin temperature has proved to be unreliable. This is due to a number

of factors, including the environmental temperature, the position of the extremities, the amount of food taken, and the basal metabolic rate (Roth and Sheard, 1950; Roth, 1951). Inadequate control of these sources of error, together with the use of different methods of investigation, may explain the diverging opinions on the influence of smoking upon the peripheral circulation in the extremities. The vasoconstrictor effect of nicotine on the extremities appears, however, to be limited to the small vessels of the skin, at least in doses similar to the amounts absorbed on smoking.

CHAPTER III

The Electrocardiogram in Tobacco-Smoking

Ssalischtschef and Tschernogoroff (1929) were the first to examine the effect of tobacco-smoking on the electrocardiogram in man. Four healthy students aged 20 to 22 years smoked cigars with inhalation of the smoke until signs of intoxication appeared. Tachycardia was a feature of all four cases, but arrhythmia developed in none of them. The electrocardiogram showed no characteristic changes, but in one case the T-waves were flattened by 2 mm. Two years later (1931) a similar study carried out on 13 healthy young subjects was published. All of them showed an increase of 14—80% in the heart rate during smoking. In a 19-year-old non-smoker the heart rate decreased suddenly from 74 to 52 beats per minute after about 30 minutes' smoking: the bradycardia developed in connection with the appearance of the signs of intoxication. In another case sino-auricular block developed, accompanied by signs of intoxication. The T-waves showed no characteristic changes, and in only in one of the thirteen cases was there a 2 mm. decrease in the height of the T-waves. The tachycardia induced by smoking was considered to be evidence of general sympathetic stimulation.

The influence of smoking and nicotine on the electrocardiogram has since been investigated by Graybiel, Starr, and White (1938), Horner and Szanto (1938), Segal (1938), Mattioli (1942), Reindell and Winterer (1942), Evans and Stewart (1943), Roth, McDonald, and Sheard (1944), von Ahn (1946, 1947, 1949), Levy, Mathers, Mueller, and Nickerson (1947), Boyle, Wegria, Cathcart, Nickerson, and Levy (1947), and Bryant and Wood (1947).

The typical electrocardiographic findings in ordinary cigarette smoking are, according to these authors, an increase in the heart rate by 10—25 beats per minute, and a flattening of the T-waves by not exceeding 1—2 mm. in the standard limb leads. Segal found that 'commercially denicotinized' cigarettes had the same effect on the electrocardiogram as ordinary cigarettes, i.e. they contained enough nicotine to produce electrocardiographic changes. Levy et al. arrived at the same result in tests with ordinary and 'denicotinized' cigarettes. Evans and Stewart examined the influence of ordinary, 'commercially denicotinized', and fully denicotinized cigarettes on the electro-

cardiogram, and found no difference between the three types of cigarette. They noted during smoking a maximum lowering of 1 mm. in the T-waves, and a simultaneous quickening of the heart rate. According to them, nicotine could not possibly be responsible for the electrocardiographic changes, since these were the same whether fully denicotinized or ordinary cigarettes were smoked. Roth et al., however, found that intravenous injection of 2 mg. of nicotine produced an increase in the heart rate by 30—40 beats per minute, and a flattening of the T-waves by 1—3 mm. in all leads. The smoking of ordinary cigarettes had a similar effect, though less pronounced. Corn-silk cigarettes had no effect on the electrocardiogram. Mathers, Patterson, and Levy (1949) state that the immediate effect on the circulation produced by smoking ordinary cigarettes is due to nicotine. The smoking of cigarettes containing only 0.23% of nicotine (i.e. 1/9 of the nicotine content of an ordinary cigarette) causes a significant increase in the heart rate.

von Ahn (1946, 1947) examined the influence of smoking on the electrocardiogram in habitual smokers (Group I), non-smokers and recent smokers (Group II). All subjects of the two groups chain-smoked until signs of intoxication occurred. In Group I, comprising 37 habitual smokers, there was an average increase in the heart rate of 15 beats per minute during the smoking-test. The T-waves showed in most cases a slight flattening of *circa* 1 mm. or less in Leads I, II, and III, and in Lead IVR a maximum flattening of 3 mm. Only in two cases did smoking provoke more pronounced electrocardiographic changes: in the first there was a transient pronounced flattening of the T-wave in Lead I and an increase in the heart rate from 58 to 83 beats per minute; in the second, the smoking of four cigarettes produced a significant flattening of the T-waves in Leads II and III (T in Lead III became diphasic), there was a 1 mm. depression of the S-T segment in Leads II and III, and the heart rate increased from 70 to 96 beats per minute. In Group II, in which 10 of the 23 subjects were non-smokers, an average increase in the heart rate of 24 beats per minute was noted. The T-waves exhibited in 18 of the cases a constant comparatively marked flattening, varying in Lead I from 0.2 to 2.3 mm., in Lead II from 0.5 to 4.4 mm., and in Lead IVR from 2.0 to 7.3 mm.

Segal has shown that the increase in the heart rate usually associated with smoking becomes less marked with increasing age. In von Ahn's Group I the subjects ranged in age from 16 to 73 years, and 19 of them were aged 40 years or more. In Group II 22 subjects ranged in age from 13 to 27 years, and only one was 40 years old. It is probable that the difference in average age between the two groups was the reason why the electrocardiographic changes on smoking were considerably more marked in Group II than in Group I. There was in Group II a considerably

more significant increase in the heart rate during smoking than in Group I. As will be seen later, a flattening of the T-waves occurs physiologically with increasing heart rate, and is proportional to it. There is no basic difference between the electrocardiographic reaction to smoking in smokers and non-smokers (Boyle et al.), or between patients with cardiac disease and normal subjects (Levy et al.).

It has been generally agreed that tobacco-smoking and nicotine provoke angina pectoris in patients with coronary disease. It is therefore of special interest to observe the electrocardiograms of these patients during smoking or after the injection of nicotine. Mattioli (1942) observed extrasystoles, negative and diphasic T-waves in Leads I and II, and depression of the S-T segment in patients with coronary disease on smoking. Bryant and Wood (1947) recorded electrocardiograms immediately after the smoking of two cigarettes in 16 patients with coronary disease. Two patients developed typical anginal pains with simultaneous and pathological changes in the electrocardiogram identical with those seen in myocardial ischaemia. In the other 14 patients there was an average increase in the heart rate by 10 beats per minute. The T-waves decreased in height by 1—2 mm., but otherwise there were no changes in the electrocardiogram.

von Ahn (1949) examined the influence of cigarette-smoking on the electrocardiogram in 30 patients with coronary heart disease, of whom 20 had angina pectoris. 23 of the patients showed clinical evidence of serious coronary heart disease with pronounced pathological electrocardiographic changes at rest. The subjects were made to chain-smoke to the stage of near-intoxication, which was reached after about 45 minutes' smoking. Electrocardiograms were recorded at intervals of about 3 minutes throughout the smoking-test. In only two of the patients with angina pectoris did smoking precipitate an anginal attack. In one of these cases (which will be described in detail further on) severe but reversible pathological electrocardiographic changes occurred simultaneously with the anginal pains; in the second, whose electrocardiogram at rest showed moderately pronounced left ventricular strain, these changes were still more accentuated during the smoking-test. In a third case frequent homologous ventricular extrasystoles, sometimes as coupled beats, were recorded at the stage of intoxication. In none of the other cases was any disturbance of rhythm noted, and the electrocardiogram was unchanged after smoking. The heart rate increased by an average of 11 beats per minute after smoking.

Boyle, Wegria, Cathcart, Nickerson, and Levy (1947) studied the influence of pure nicotine on the electrocardiogram of 46 subjects 18 of whom were healthy, 24 had coronary heart disease, and 4 a peripheral vascular disease. The nicotine preparation consisted of nicotine bitartrate in a dose of 2 mg., corresponding to approximately 0.6 mg. of free base. After intravenous

injection of nicotine, significant electrocardiographic changes were observed in only four of the patients with coronary disease; two of these patients developed angina pectoris simultaneously with the changes in the electrocardiogram. Partial or complete inversion of the T-waves and depression of the S-T segment by 1 mm. or more were regarded as significant. The heart rate increased by an average of 19 beats per minute in the normal subjects and 14 beats per minute in the cardiac patients. The blood sugar was determined before and after the injection of nicotine, but no consistent changes were noted. According to the authors, it is improbable that augmented adrenal secretion was responsible for the cardiac changes.

Thus neither smoking nor the injection of nicotine produces any significant electrocardiographic changes in normal subjects or in the majority of cardiac patients. But what happens during exercise tolerance tests?

Dietrich and Schimert (1939), using a cycle ergometer, performed exercise tests on 17 subjects before and after the smoking of cigarettes, and electrocardiograms were taken. Most of the subjects did not notice any decrease in physical efficiency after smoking; some, however, felt their performance was impaired by smoking, and others thought it was improved. As far as can be seen from the authors' short account of these investigations, smoking did not accentuate the electrocardiographic changes noted in the pre-smoking exercise tolerance tests. Reindell and Winterer (1942) investigated the influence of smoking on the electrocardiogram in 60 subjects after tolerance tests consisting of 50 successive knee-bendings. Half of the subjects were healthy persons, the remaining 30 having previously shown evidence of cardiac disease. Two tests were performed on each subject and on separate occasions. In one case an interval of more than three months elapsed between the tests. One test was performed without previous smoking, the other after the subject had smoked 14 to 20 cigarettes earlier that day. The amplitude of the T-waves was compared in the two tests: in the smoking tests the T-waves showed considerably more marked flattening than in the non-smoking tests, and diphasic or negative T-waves appeared in Leads II and III. They therefore concluded that tobacco can cause circulatory disturbances and impairment of cardiac efficiency, and possibly by some nervous mechanism influence the coronary circulation.

Closer examination of the heart rate in the pre- and post-smoking tests, however, reveals a considerable difference between the two. In one case (Case 8) the heart rate was 64 and 58 beats per minute at 1 and 3 minutes respectively after the pre-smoking test. The corresponding rates after the post-smoking test were 114 and 110 beats per minute respectively. The rates for another case (Case 36) were 80 and 79 beats per minute respectively (pre-smoking test), and 130 and 122 beats per minute (post-smoking test). The heart rate was thus considerably faster after the post-smoking exercise tole-

rance tests than after the pre-smoking tests. In a third case (Case 3), however, the flattening of the T-waves was more significant after smoking than during abstinence, although there was no difference in heart rate; but both tests were performed at an interval of 4 days, so it is therefore possible that the now well recognized day-to-day variations in the T-waves may have been responsible for the difference in amplitude.

von Ahn (1946, 1947) has also carried out exercise tolerance tests before and after chain-smoking. In some of the post-smoking tests the heart rate was considerably faster than in the corresponding pre-smoking tests, but no definite pathological changes in the electrocardiogram were noted after the post-smoking tests.

Arrhythmias in the form of extrasystoles have often been described in heavy smokers. Other disturbances in rhythm which can be referred to tobacco-smoking are rare. Neuhof (1916) describes one case of auricular flutter, one of auricular fibrillation, and two of sino-auricular block. Laslett (1921) has seen two cases of paroxysmal auricular fibrillation and two cases of paroxysmal tachycardia in heavy smokers. Both authors consider the cases they describe to be due to excessive tobacco-smoking.

In a few patients with coronary heart disease tobacco-smoking and injection of nicotine can precipitate angina pectoris and pathological electrocardiographic changes which are certainly evidence of myocardial ischaemia. It should be emphasized that these cases are rare; they will be discussed at greater length in the chapter on Tobacco Angina. As above described, smoking results in most cases in an increase in the heart rate with a simultaneous flattening of the T-waves not exceeding 1—2 mm. in the standard limb leads. According to most investigators, these electrocardiographic changes are not due to coronary insufficiency (Graybiel et. al.; Roth et al.: von Ahn; Levy et al.). On the contrary, it has been maintained that the changes are evidence of increased sympathetic tone (Ssalischtschef and Tschernogoroff; Graybiel et al.: von Ahn). This pattern of electrocardiogram typical of increased sympathetic tone is often to be found in connection with heavy smoking; it is characterized by tachycardia, high P-waves, and lowered T-waves (von Ahn 1947). Graybiel et al. found the ECG after smoking to have a striking similarity to that obtained after intravenous injection of 2 mg. of atropine. They also found that the flattening of the T-waves after smoking was not influenced by amyl nitrite, which suggests that the cause is not coronary insufficiency.

Summary

In both normal persons and cardiac patients tobacco-smoking and injection of nicotine generally induce an increase in the heart rate with simultaneous slight flattening of the T-waves. These changes have been considered by some authors to be the result of increased sympathetic tone. Others have suggested a coronary origin. In some patients with coronary disease, however, tobacco-smoking and nicotine can precipitate acute coronary insufficiency

CHAPTER IV

General Critical Views on the Tobacco Problem

As will have been seen from Chapter I, many authors have claimed that tobacco-smoking causes coronary spasm and precipitates angina pectoris. The clinical conception of the unfavourable influence of tobacco on the coronary circulation has been partly based on experiments on animals (Chapter II). Investigations showing the constrictive effect of tobacco on the coronary vessels have often been quoted, whereas less attention has been drawn to investigations in which it has been shown that nicotine may also have the effect of dilating the coronary vessels. From a clinical point of view great care must be exercised about drawing conclusions based on animal experiments. The amounts of nicotine employed in these experiments have often been much larger than those absorbed during smoking (Chapter II).

It is quite common for excessive tobacco-smoking to produce chest pains of an anginal type. In young persons with otherwise clinically normal hearts such pains also occur, but subside completely after a period of non-smoking. This syndrome of pains, which goes under the name of tobacco angina, will be discussed later in this work.

Transient electrocardiographic changes such as flattened or inverted T-waves and depression of the S-T segment have been described in smokers (Strauss, Lickint). These changes in the electrocardiogram have earlier been ascribed to coronary spasm produced by vagal stimulation, and have been regarded as evidence of the disturbing influence of tobacco on the nervous regulation of the coronary vessels (Strauss; Hochrein; Reindell and Winterer). This explanation has been taken for granted in the light of nicotine's stimulatory effect on the vagus and constrictive effect on the coronary vessels which have often been alleged by the pharmacologists. During recent years, however, it has been proved that the T-waves can show spontaneous and considerable variations from day to day and hour to hour. This feature has been ascribed to changes in autonomic tone (Nordenfelt, 1941). The amplitude of the T-wave is dependent on different factors, among them the heart rate. It has actually been shown that the T-waves become smaller as the heart rate quickens (Sjöstrand, 1950; Björkman, 1951); and in persons with clinically

normal hearts the T-waves may become isoelectric, or even negative, when the heart rate is rapid enough. Many of the electrocardiographic changes previously believed to be pathological are today counted as spontaneous physiological variations. Particularly marked spontaneous variations in the pattern of the electrocardiogram appear in emotionally unstable but otherwise normal persons (Nordenfelt). These persons have a labile heart rate and develop tachycardia after sundry physical and mental exertions, and often very pronounced flattening of the T-waves appears simultaneously with the tachycardia. Smoking produces increased heart rate with flattening of the T-waves (Chapter III). This flattening need by no means be evidence of disease, such as coronary insufficiency, but can be satisfactorily explained by increase in the heart rate due to smoking. In young persons (von Ahn, 1947), and in patients suffering from neurocirculatory asthenia, smoking can induce marked tachycardia with striking electrocardiographic changes. Graybiel et al. found even negative T-waves in young emotionally unstable persons on smoking. In many cases the electrocardiogram assumes after smoking a pattern similar to that seen in increased sympathetic tone: increased heart rate; conspicuously high P-waves; sometimes depression of the S-T segment; and lowered, diphasic, or negative T-waves in Leads II and III. As a rule, the younger the subject the more susceptible he is to nicotine, and the more pronounced is the increase in the heart rate and the flattening of the T-waves on smoking. According to the modern view, many of the 'pathological' changes in the electrocardiogram ascribed in the past to coronary insufficiency induced by smoking might be classified within the limits of physiological variations.

As described in Chapter II, Burn et al. have shown that antidiuretic hormone from the posterior pituitary is liberated by smoking. It has been assumed that this hormone is identical with the vasoconstrictor hormone (Pitressin), which has a vigorous constrictor effect on the coronary vessels (Morawitz and Zahn; Rössler). Cases of heart infarction after injection of pitressin are described (Mills, Burchell, Parker, and Kirklin, 1949). Tobacco-smoking and injection of nicotine can, however, provoke acute coronary insufficiency (Chapter III), but such cases are very rare. Still more rare are the fatal cases in close connection with smoking which have been reported (Fiessinger, 1923; Littman and Barr, 1952). On the other hand, I do not know of any case where smoking in itself has induced heart infarction, neither has heart infarction been described in any of the many cases of acute nicotine poisoning due to insecticides, where very large amounts of nicotine have been involved (von Ahn, 1952, 1953). It may be questioned whether tobacco-smoking has indeed the deleterious effect on the vasomotor mechanism of the coronary vessels ascribed to it in the past (Hochrein; Reindell and Winterer). If this were so one might reasonably expect freqeunt

cases of angina pectoris and heart infarction in close relation to tobacco-smoking, especially considering the vast spreading of the tobacco habit even in patients suffering from coronary disease. Clinical experience, however, does not support the view that smoking constricts the coronary vessels to the extent that coronary insufficiency is the usual result in cardiac patients. On the contrary, it is accepted that most cardiac patients can smoke in moderation without suffering increased disability (Levy et al., 1947). In most patients with angina pectoris no direct relationship between the tobacco habit and anginal attacks is to be found (von Ahn, 1949). This is astonishing, since these cardiac patients have a decreased coronary reserve, and the possible constrictor effect of tobacco on the coronary vessels should be particularly apparent in them. Even if the majority of the coronary vessels are severely sclerosed and rigid and are incapable of constriction the arterioli are intact. Arteriolosclerosis does not occur in the heart, and it is possible that these small arteries could be constricted by nicotine, with acute coronary insufficiency as result. Hirsch (1950) has stressed the particular significance of the coronary arterioles in the pathogenesis of heart infarction. Most patients suffering from severe heart disease tolerate a smoking-test of 45 minutes' duration without suffering immediate disabilities or, as far as is known, after-effects (von Ahn, 1949). This does not conform with the theories about the disturbing influence of tobacco on the coronary circulation.

As we have seen in Chapter II, smoking undoubtedly produces peripheral vasoconstriction in the extremities, limited, however, to the small vessels of the skin (Abramson et al.). But it has still not been proved that tobacco-smoking in man usually has a clinically significant effect on the coronary vessels. This problem will be discussed in the next chapter.

CHAPTER V

The Problem

As we have seen in Chapter III, under ordinary circumstances smoking produces only a slight or moderate increase in the heart rate and a slight flattening of the T-waves. These changes in the electrocardiogram can in no way be considered pathological, nor do any definite pathological changes appear in the electrocardiogram after smoking plus exercise. Dietrich and Schimert (1939), who carried out post-smoking exercise tolerance tests by means of bicycle ergometer, have also carried out smoking tests in a low-pressure chamber. Eleven subjects smoked 3—6 cigarettes at a low pressure corresponding to a height of 5,000 metres. Electrocardiograms were taken before and after smoking. In ten of the eleven subjects no electrocardiographic changes suggesting impaired coronary flow occurred; in the remaining subject there was a slight flattening of the T-waves in Lead II. According to the authors, nicotine did not impair the coronary flow in spite of these extreme circumstances (low pressure). The influence of smoking on the hypoxic heart has gained further interest owing to experiments carried out by Bellet, Kershbaum, Meade, and Schwartz (1941), who showed, by experiments on dogs, that the effect of tobacco-smoking and nicotine was more pronounced on hearts with artificial infarction than on intact hearts. When heart infarction had been induced by ligature of a coronary artery the experimental animals developed pronounced electrocardiographic changes following a dose of nicotine which was only a quarter of that required to produce slight changes in intact animals. I now ask whether smoking or injection of nicotine during hypoxia can produce pathological changes in the electrocardiogram in man. Hypoxia is believed to develop in the myocardium on inhalation of a gas mixture deficient in oxygen (Akesson and Malmström, 1945). The organism attempts to compensate for the oxygen deficiency partly by increasing the heart rate and the coronary flow (Dietrich and Schimert). Hypoxia or anoxia leads to dilatation of the coronary vessels by 200—300% (Gregg, 1950), the maximum dilatation occurring when the arterial oxygen saturation has decreased to 50% of the normal value. The coronary reserve may be reduced considerably before the function of the heart substantially deteriorates and pathological changes in the electrocardiogram develop. Wegria et al. (1949) found in experiments on dogs that a reduction in the

coronary flow of 10—35% does not as a rule produce any changes in the electrocardiogram; a reduction of 35—70% results in 'slight' electrocardiographic changes; and a reduction of 70—100% produces changes which are always pronounced. The normal organism thus possesses exceptional powers of compensating hypoxia and imminent coronary insufficiency. During hypoxia an alteration in the irritability of the heart muscle occurs, on which arrhythmias of different types may appear — e.g. extrasystoles, auricular fibrillation (Smith and Wilson, 1944), and, during extreme hypoxia, even ventricular fibrillation (Dietrich and Schimert). Auricular fibrillation occurs especially readily on a combination of hypoxia with vagal stimulation (Smith and Wilson; Grant, Gertler, and Terroux). Nicotine can induce auricular fibrillation even in the presence of normal oxygen levels, as has been described in dogs (Clerc and Deschamps, 1922, 1923) and also in acute nicotine poisoning in man (von Ahn, 1952, 1953). During hypoxia nicotine should be able more easily and in smaller doses to produce arrhythmias.

The effect of nicotine is, as we have seen in Chapter II, very complex, and not easily summarized. It may be said to disturb in different ways the normal balance between coronary flow and cardiac efficiency. It might be expected that cardiac efficiency would be impaired particularly during hypoxia. If nicotine causes coronary constriction or 'spasm' this might impair the physiological compensatory dilatation of the coronary vessels which occurs during hypoxia. Nicotine also produces an indirect effect upon the coronary flow via humoral agents such as pitressin, adrenaline, and probably also noradrenaline. A stimulation of the suprarenals results in a simultaneous secretion of adrenaline and noradrenaline (Lund, 1951). Haimovici (1948) is of the opinion that nicotine may also have a direct constrictive effect on the blood vessels. Concerning the peripheral vessels, Rapaport et al. (see Chapter II) maintain that smoking produces peripheral vasoconstriction only by way of the sympathetic fibres, and not by means of humoral agents. It may be questioned whether this also holds good for the coronary vessels. Experiments by Burn et al. (Chapter II), however, show that smoking can cause coronary constriction by releasing posterior pituitary hormone. At the same time nicotine produces increased secretion of adrenaline, and probably also of noradrenaline, both of which have the effect of dilating the coronary vessels. *What is the net effect?* The effect of an intravenous injection of adrenaline only continues a few minutes, but the effect of an intravenous injection of posterior pituitary hormone has a duration of 10—30 minutes (Sollman).

The influence of nicotine on coronary flow and cardiac efficiency of a heart *in situ* is thus very complex. In the following, the influence of tobacco-smoking and nicotine on the electrocardiogram during the clinical hypoxia test will be discussed.

CHAPTER VI

Material and Methods

Material

The series consists of two groups arranged according to age.

Group I is composed of 59 subjects (nos. 1—59) — 41 soldiers ranging in age from 20 to 24 years and 18 medical students aged 23 to 28 years. Of the 59, 31 were smokers (nos. 1—29, 57, 59) and 28 non-smokers (nos. 30—56, 58). A soldier aged 20 (no. 60) with no cardiac disability proved to have a pathological electrocardiogram during hypoxia, and was therefore considered to have possible myocardial damage: he is not included in the statistical analysis but remains in the series as a demonstration of the influence of nicotine on the electrocardiogram. None of the other subjects showed evidence of heart disease on ordinary physical examination or in the electrocardiograms at rest and during hypoxia.

Group II includes 27 subjects (nos. 101—127) ranging in age from 38 to 57 years. Of them 19 were aged 45 years or more, and 21 were smokers and 6 non-smokers. Physical examination and electrocardiograms at rest and during hypoxia showed no evidence of heart disease, except for slight or moderate hypertension in 4 cases. The blood-pressures at rest in these cases (aged 46, 54, 48, and 53 years) were 138/100, 150/100, 170/100, and 186/116 mm. Hg. In all the others the blood-pressure was below 150/100 mm. Hg. at rest. None of the subjects complained of anginal pains at rest or on exertion. Two claimed to become moderately out of breath on physical exertion, and the others considered their physical efficiency to be normal for their age. Only six of the subjects had no history of disease; 3 had had rheumatic fever, and one scarlatina; the others gave histories of pleurisy, pneumonia, peptic ulcer, acute nephritis, otitis, or appendicitis. On examination all the subjects were in good health.

Methods

The subjects were asked to come to the different tests in a fasting state, or to eat as little as possible beforehand. The smokers abstained from smoking for at least 3—4 hours before each test. Before the tests the subjects rested 30—40 minutes on a comfortable couch.

All experiments were performed during the course of 2½ years.

The Different Experiments

Group I

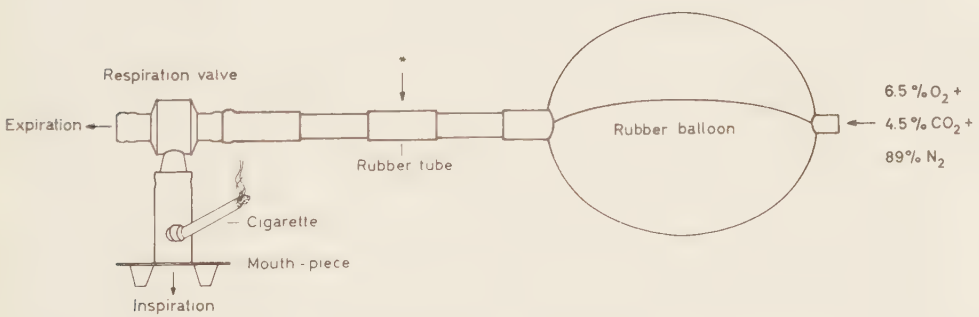
This group underwent control tests, cigarette- and cigar-tests, and intravenous injection of nicotine during hypoxia. The first electrocardiogram was taken after 6 minutes' hypoxia, when the respiratory rate, the heart rate, and arterial oxygen saturation of the blood had become established at constant levels. Electrocardiograms were subsequently taken after 10, 14, and 17 minutes' hypoxia. The blood-pressure was registered immediately after each electrocardiogram. The hypoxia test lasted about 20 minutes, and was ended by breathing pure oxygen for 2 or 3 minutes.

Controls

Possible changes in the electrocardiogram occurring at rest during hypoxia only were established by means of a control test without smoking or injection of nicotine. At least one control test was performed on each individual, except for four, where control tests were not done. 15 of the subjects underwent two control tests on different days, and during one of these tests 10 ml. of physiological saline was injected intravenously (see below, Nicotine-tests I).

Smoking-tests (cigarette)

Smoking-tests were performed on 26 smokers (nos. 1—26) and 20 non-smokers (nos. 30—45, 51—54). During the test each individual smoked one cigarette, which was fixed in a special holder on the mouthpiece of the respiratory valve (see fig. below).



Arrangement of the apparatus

With every breath the subject inhaled a certain amount of tobacco-smoke. If the subject had difficulty in inhaling he was assisted by compressing the

rubber tube at * during the inspiration. The smoking-test began after 9 minutes' hypoxia and lasted 8 minutes, thus ending after 17 minutes' hypoxia. The cigarette employed had a nicotine content of 1.74%.

Smoking-tests (cigar)

Cigar-tests were carried out on 6 smokers (nos. 1—4, 18, 29), and 14 non-smokers (nos. 34—42, 45—49). The test was performed exactly in the same way as the cigarette test. The subjects smoked 3—4 cm. (2—3 g. of tobacco) of a cigar (Flor de Vallez) the total weight of which was 6 g. The nicotine content of the cigar was 2.58%.

Nicotine-tests

Since the amounts of nicotine absorbed during the smoking tests could not be determined, experiments were also performed with pure nicotine in a known dose. The doses of nicotine were chosen so as to correspond approximately to the amounts of nicotine probably absorbed on the smoking of one cigarette or 1 g. of cigar tobacco.

Nicotine bitartrate was injected intravenously in two different doses: 1 mg. of nicotine (free base) — nicotine-tests I; or 3 mg. of nicotine (free base) — nicotine-tests II.

In *nicotine-tests I,* 1 ml. of nicotine solution (= 1 mg. of alkaloid) was diluted with 9 ml. of physiological saline. The injection was made as uniformly as possible over a period of 3 minutes, beginning after 9 minutes' hypoxia and ending after 12 minutes' hypoxia. 23 tests were performed (nos. 1, 2, 4, 16, 18—20, 23, 27, 33, 34, 38—42, 45, 50—54). Controls were done in 15 of the subjects, 10 ml. of physiological saline being injected.

In nicotine-tests II, 3 ml. of nicotine solution (= 3 mg. of alkaloid) was diluted with 17 ml. of physiological saline to 20 ml. Injection was begun after 9 minutes' hypoxia and completed after 17 minutes' hypoxia. 20 tests were performed (nos. 1—4, 14, 27—29, 33—37, 39—41, 50, 52—54).

In addition some tests were carried out with injection of adrenaline, dihydroergotamine, and atropine during hypoxia.

Exercise tolerance tests using a bicycle ergometer

In order to study the effect of exercise on the electrocardiogram during hypoxia 18 bicycle ergometer tests were performed (nos. 1, 3, 13, 18, 25, 27, 28, 34, 50 –53, 55, 55—59). The load amounted to 2 kg., and the average work to 80 kgm. per minute for 8 minutes. The tests were performed in order to produce a physiological increase in the heart rate of about the same degree as that in the smoking and nicotine tests.

Group II

Controls

Controls were carried out on all individuals and in the same way as in Group I.

Smoking-tests

To begin with, 10 preliminary cigarette-tests were performed, without obvious effect on the heart rate or electrocardiogram. Subsequently, therefore, cigar-tests only were done. The method was as in Group I.

In this group no nicotine tests and only one bicycle ergometer tolerance test (no. 104) during hypoxia were done.

The hypoxia test was performed with a gas mixture consisting of 6.5% O_2, 4.5% CO_2, and 89% N_2 (Malmström, 1947), which gives a practically constant oxygen saturation during the hypoxia test from the 5th or 6th minute.

The electrocardiograms were recorded by means of a 'Clinic Apparatus' from AB. Elema-Järnhs, Stockholm, with which 4–5 leads can be registered synchronously. In addition to the usual three leads from the extremities (Leads I, II, and III), three chest leads (CR_2, CR_4, and CR_7) were recorded. The heights of the P- and T-waves were measured from the P-Q level to within .25 mm. The P-Q level is, however, often not the true isoelectric level, since it embraces the auricular T-wave. (This T_a-wave is very low in the standard limb leads (Lepeschkin, 1951); it may in certain cases be a source of error when measuring the S-T level — see Malmström, 1947.) The height of the S-T level from the P-Q level was measured at a point .04 secs. after the RS-T junction (J) according to Goldberger (1953). At least three P- or T-waves and S-T segments were measured, and the mean was estimated.

Oximeter readings

The oxygen saturation of the blood during the hypoxia test was measured continuously by means of an oximeter (Millikan). After the subject had breathed pure oxygen during 7–10 minutes the oximeter was set at 100% oxygen saturation, which was thus the initial reading.

The oximeter registers only changes in the arterial oxygen saturation, and not absolute values. Concerning the oximeter and its use, see Lindgren (1948), Comroe (1950), and Zijlstra (1951). One condition for the oximeter to register correctly is that the variation in the thickness in the pinna is automatically compensated by photoelectric cells in the earpiece. On vasoconstriction in the pinna this automatic compensation may be inadequate. If nicotine produces vasoconstriction in the pinna this may involve a source of error.

The oximeter has registered correctly in all smoking-tests (Group I), in 21 of the 23 tests with 1 mg. of nicotine, and in 14 of the 20 tests with 3 mg. of nicotine. In addition, in all smoking-tests of Group II the oximeter registered correctly and returned to the initial value of 100% oxygen saturation after 2—3 minutes breathing pure oxygen. The thickness of the pinna was repeatedly checked during the hypoxia tests by switching over from the saturation position to the ear thickness position.

Determination of the Arterial Oxygen Saturation by means of Pulfrich's Step Photometer

In order to check the oximeter readings and to obtain absolute values the arterial oxygen saturation was determined with Pulfrich's Step Photometer according to Jonxis' method (1943). Blood samples were taken from the brachial artery under local anaesthesia. The oxygen saturation was determined in 24 of the cigarette-tests and in 10 of the cigar tests, samples being taken about one minute before and one minute after the end of the smoking test. The oxygen saturation was calculated from Jonxis' formula

$$\frac{E_r - E_s}{E_r - \frac{E_r}{C}} \cdot 100,$$

in which E_r is the extinction for reduced haemoglobin and E_s the extinction for non-reduced haemoglobin. C is an apparatus constant, and was obtained from the ratio $E_r : E_s$ measured on saturated blood taken by arterial puncture from 20 different individuals (Group I) after at least 10 minutes breathing pure oxygen: on the basis of these measurements C was calculated to 5.1. As an additional check of the step photometer, simultaneous determinations of the arterial oxygen saturation in hypoxic blood from 17 different tests were performed by van Slyke's gasometric method. The oxygen saturation in the hypoxic blood varied from 84 to 56%. It was proved by these determinations that the values obtained with the step photometer were $1.51\% \pm 0.44$ lower than those found by van Slyke's method ($t = 3.403$, $0.001 < P < 0.01$). The error of method in the spectrophotometric determinations is 0.75% oxygen saturation according to the formula derived from Czuber

$$\delta_e = \sqrt{\frac{\Sigma\, \delta_2^2}{2 \cdot N_2}} \quad \text{(Enghoff, 1937)}$$

δ_2 is the difference between two single determinations and N_2 the number of double determinations. 84 double determinations were done. 64 determinations of the arterial oxygen saturation were done using the step photometer and the oximeter simultaneously as a check of the oximeter readings. The

oximeter showed values on an average 7.3% ± 0.95 lower than those given by the step photometer (S = 7.6).

Some carbon monoxide is absorbed and a certain amount of carboxyhaemoglobin is produced on smoking. There is a certain source of error in these spectrophotometric determinations, owing to the fact that carboxyhaemoglobin, oxyhaemoglobin, and reduced haemoglobin have different absorption maxima. The amount of carboxyhaemoglobin compared to that of oxyhaemoglobin and reduced haemoglobin in these determinations is however too small to influence the results.

Statistical Methods

In the statistical analysis of the changes in oxygen saturation and blood-pressure noted during the various tests, the following statistical methods and terms are used (Dixon and Massey, 1951).

X_i is the difference between the reading after 6 and 18 minutes' hypoxia in the same individual during the various tests.

Z_i is the difference between the change taking place between the 6th and 18th minutes in one experiment and the change between the 6th and 18th minutes in another experiment on the same individual, thus,

$$(X_{i\alpha} - X_{i\beta}) = Z_i$$

i indicates the i^{th} individual.

Arithmetical mean $\bar{X} = \frac{1}{N} \sum_{i=1}^{N} X_i$

The error of the mean $s_{\bar{x}} = \sqrt{\frac{s^2}{N}}$

in which $s^2 = \frac{\sum_{i=1}^{N} (X_i - \bar{X})^2}{N - 1}$ is the variance.

The analyses were performed under null hypothesis. As the number of observations in almost all cases is less than 30, the hypothesis was tested with Student's t-test,

$$t = \frac{\bar{X}}{\sqrt{\frac{s^2}{N-1}}} =$$

P is the probability that the difference observed is due to chance on (N — 1) degrees of freedom.

$P < 0.001$ denotes that the difference is highly significant. $0.001 < P < 0.01$ denotes that the difference is significant. $0.01 < P < 0.05$ denotes that the difference is probably significant.

CHAPTER VII

The Arterial Oxygen Saturation and the Blood-Pressure in the Different Experiments

Checking of Experimental Conditions

The oximeter values after 6 minutes hypoxia are given in table 1.

Table 1.

	N	$\bar{X}$	s	$s_{\bar{X}}$
Controls	88	59.68 %	7.185	± 0.770
Nicotine I	21	61.81 %	6.728	± 1.4632
Nicotine II	14	61.07 %	5.469	± 1.4616
Cigar-tests	46	62.37 %	5.848	± 0.872
Cigarette-tests	46	59.22 %	8.066	± 1.203
The whole series	215	60.46 %		

There is no significant difference between the means for oxygen saturation in the different tests.

The Changes in Arterial Oxygen Saturation as Measured with the Oximeter between the 6th and 18th Minutes of the Tests

Table 2. *Controls.*

		N	$\bar{X}$	s	$s_{\bar{X}}$	|t|	P
Group I	Smokers	31	— 3.419 %	3.7839	± 0.6796	4.950	< 0.001
	Non-smokers	30	— 2.767 %	2.7752	± 0.5067	5.368	< 0.001
Group II		25	— 1.720 %	3.3356	± 0.6671	2.526	0.01 < P < 0.02

The fall in oxygen saturation is highly significant in Group I, and probably significant in Group II.

Table 3. *Cigarette-tests.*

		N	$\bar{X}$	s	$s_{\bar{X}}$	|t|	P
Group I	Smokers	27	— 2.654 %	3.8464	± 0.7402	3.449	$0.001 < P < 0.01$
	Non-smokers	19	— 1.947 %	3.2739	± 0.7511	2.523	$0.01 < P < 0.02$

The fall in oxygen saturation is significant in smokers, and probably significant in non-smokers.

Table 4. *Cigar-tests.*

	N	$\bar{X}$	s	$s_{\bar{X}}$	|t|	P
Group I	21	— 3.711 %	4.1357	± 0.9025	4.012	< 0.001
Group II	25	— 2.280 %	3.1161	± 0.6232	3.585	$0.001 < P < 0.01$

The fall in oxygen saturation is highly significant in Group I, and significant in Group II.

Table 5. *Nicotine-tests I.*

	N	$\bar{X}$	s	$s_{\bar{X}}$	|t|	P
Group I	21	+ 0.2381 %	4.3578	± 0.9509	0.2443	$0.8 < P < 0.9$

The mean oxygen saturation shows no significant change.

Table 6. *Nicotine-tests II.*

	N	$\bar{X}$	s	$s_{\bar{X}}$	|t|	P
Group I	14	0 %	2.3859	± 0.6377	0	

The mean oxygen saturation shows no change.

Table 7. *The difference between the changes in oxygen saturation in cigarette-tests and controls.*

		N	$\bar{Z}$	s	$s_{\bar{Z}}$	|t|	P
Group I	Smokers	29	+ 0.6207 %	4.6323	± 0.8602	0.709	$0.4 < P < 0.5$
	Non-smokers	24	+ 0.1667 %	3.5345	± 0.7215	0.226	$0.8 < P < 0.9$

There is no significant difference between the changes in oxygen saturation in the two series.

Table 8. *The difference between the changes in oxygen saturation in nicotine-tests I and in controls.*

	N	$\bar{Z}$	s	$s_{\bar{Z}}$	$\lvert t \rvert$	P
Group I	29	+ 3.586 %	4.4118	± 0.8193	4.282	< 0.001

There is thus a highly significant rise in oxygen saturation in nicotine-tests I compared with the controls.

Table 9. *The difference between the changes in oxygen saturation in nicotine-tests II and in controls.*

	N	$\bar{Z}$	s	$s_{\bar{Z}}$	$\lvert t \rvert$	P
Group I	19	± 3.3684 %	3.3700	± 0.7731	4.240	< 0.001

Here too the rise in oxygen saturation is highly significant in comparison with the controls.

Table 10. *The difference between the changes in oxygen saturation in cigar-tests and in controls.*

	N	$\bar{Z}$	s	$s_{\bar{Z}}$	$\lvert t \rvert$	P
Group I	18	— 0.3889	5.1118	± 1.2050	0.313	$0.7 < P < 0.8$
Group II	22	— 0.6364	4.0423	± 0.8618	0.721	$0.5 < P < 0.6$

There is no significant difference between the changes in oxygen saturation noted in the two series.

Determination of the Changes in Oxygen Saturation during the Smoking-tests, by means of Pulfrich's Step Photometer

In the *cigarette-tests* the arterial oxygen saturation was determined about 1 minute before and 1 minute after smoking with Pulfrich's Step Photometer in 24 cases. There was a fall in oxygen saturation of 1.76% ± 0.45 during the smoking-tests. The difference is statistically significant ($P < 0.001$).

In the *cigar-tests* the change in oxygen saturation was determined with Pulfrich's Step Photometer in 10 cases. There was a significant decrease of 2.28% ± 0.59 ($0.001 < P < 0.01$).

Both the oximeter and the step photometer thus gave similar values of the changes in oxygen saturation. In Group II, cigar-smoking, the values were identical (fall 2.28%).

Summary

There is no significant difference between the mean oxygen saturations measured after 6 minutes hypoxia in the different tests. Thus the experimental conditions must have been similar.

The change in oxygen saturation occurring between the 6th and 18th minutes of the different tests was established with the aid of an oximeter. The mean oxygen saturations in the *controls* showed the following falls: Group I smokers 3.4% (highly significant); Group I non-smokers 2.8% (highly significant); Group II 1.7% (probably significant). In the *cigarette-tests* (done in Group I only) there was a fall of 2.7% (significant) in smokers, and 1.9% (probably significant) in non-smokers. In the *cigar-tests* the fall in oxygen saturation was significant both in Group I and Group II (3.7% and 2.3% respectively). In the *nicotine-tests* (Group I only) there was no significant fall in oxygen saturation.

A comparison was made of the average changes in oxygen saturation in the different tests between the 6th and 18th minutes. A rise in oxygen saturation of about 3% was noted in the *nicotine-tests* compared with the controls. This is probably due to the fact that nicotine stimulates respiration, which increases in depth and rate during these tests.

The values of the changes in oxygen saturation as measured with the oximeter during the smoking-tests were comparable with corresponding values of the step photometer.

Blood-Pressure Changes during Hypoxia between the 8th and 18th Minutes in the Different Tests

Table 11. *Controls.*

		N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
Group I	Smokers	25	0.16 mm. syst.	± 1.196	0.134	$0.8 < P < 0.9$
			— 2.72 mm. diast.	± 1.190	2.286	$0.02 < P < 0.05$
	Non-smokers	20	— 1.00 mm. syst.	± 1.580	0.617	$0.5 < P < 0.6$
			— 3.90 mm. diast.	± 0.968	3.928	$P < 0.001$
Group II		27	— 6.59 mm. syst.	± 1.391	4.738	$P < 0.001$
			— 3.33 mm. diast.	± 1.245	2.675	$0.01 < P < 0.02$

In Group I there was a highly significant fall in the diastolic blood-pressure in non-smokers. In Group II there was a highly significant fall in systolic pressure, and a probably significant fall in diastolic pressure.

Table 12. *Cigarette-tests.*

	N	$\bar{X}$	$s_{\bar{x}}$	|t|	P
Group I Smokers	27	5.04 mm. syst.	± 1.009	4.995	$P < 0.001$
		— 0.30 mm. diast.	± 1.293	0.232	$0.8 < P < 0.9$
Non-smokers	19	1.47 mm. syst.	± 1.133	1.263	$0.2 < P < 0.3$
		— 0.11 mm. diast.	± 1.311	0.082	$0.9 < P < 1.0$

The systolic pressure showed a highly significant rise in smokers, but otherwise there were no significant changes in blood-pressure.

Table 13. *Cigar-tests.*

	N	$\bar{X}$	$s_{\bar{x}}$	|t|	P
Group I	22	5.55 mm. syst.	± 1.643	3.300	$0.001 < P < 0.01$
		— 2.64 mm. diast.	± 1.614	1.598	$0.1 < P < 0.2$
Group II	27	2.30 mm. syst.	± 1.463	1.572	$0.1 < P < 0.2$
		— 3.56 mm. diast.	± 1.015	3.507	$0.001 < P < 0.01$

In Group I there was a significant rise in systolic pressure, and in Group II a significant fall in diastolic pressure.

Table 14. *Nicotine-tests I.*

	N	$\bar{X}$	$s_{\bar{x}}$	|t|	P
Group I	21	0.38 mm. syst.	± 2.614	0.142	$0.8 < P < 0.9$
		— 0.76 mm. diast.	± 1.504	0.493	$0.6 < P < 0.7$

No significant change in blood-pressure was seen in this series. The standard deviation in systolic pressure is, however, conspicuously high; this is explained by a fall in systolic blood-pressure from 142 to 100 mm. Hg. in one case after injection of nicotine.

Table 15. *Nicotine-tests II.*

	N	$\bar{X}$	$s_{\bar{x}}$	|t|	P
Group I	19	4.32 mm. syst.	± 3.131	1.343	$0.1 < P < 0.2$
		2.63 mm. diast.	± 1.154	2.219	$0.02 < P < 0.05$

There was a probably significant rise in diastolic pressure. The standard deviation of the systolic values is conspicuously high in this series too, owing to a rise in blood-pressure in one case from 120/76 mm. Hg. to 170/82 mm. Hg. after injection of nicotine.

Table 16. *The difference between the changes in blood-pressure in cigarette-tests and controls.*

		N	$\bar{Z}$	$s_{\bar{Z}}$	|t|	P
Group I	Smokers	23	5.83 mm. syst. 3.30 mm. diast.	± 1.756 ± 1.522	3.248 2.119	0.001 < P < 0.01 0.02 < P < 0.05
	Non-smokers	14	2.71 mm. syst. 3.14 mm. diast.	± 1.859 ± 1.063	1.405 2.847	0.1 < P < 0.2 0.01 < P < 0.02

The difference between the changes in systolic pressure in Group I smokers and the changes in systolic pressure in the controls is significant.

Table 17. *The difference between the changes in blood-pressure noted in cigar-tests and controls.*

	N	Z	$s_{\bar{Z}}$	|t|	P
Group I	14	10.14 mm. syst. 2.14 mm. diast.	± 2.520 ± 2.639	3.878 0.718	0.001 < P < 0.01 0.4 < P < 0.5
Group II	27	8.89 mm. syst. — 0.22 mm. diast.	± 2.043 ± 1.669	4.270 0.131	P < 0.001 0.8 < P < 0.9

The systolic blood-pressure showed a significant rise in Group I and a highly significant rise in Group II.

Table 18. *The difference between the changes in blood-pressure in nicotine-tests I and in controls.*

	N	$\bar{Z}$	$s_{\bar{Z}}$	|t|	P
Group I	18	— 2.22 mm. syst. + 0.17 mm. diast.	± 4.386 ± 2.487	0.492 0.065	0.6 < P < 0.7 0.9 < P < 1.0

The difference between the blood-pressure changes in the nicotine-tests and the same changes in the controls was not significant.

Table 19. *The difference between the changes in blood-pressure in nicotine-tests II and in controls.*

	N	$\bar{Z}$	$s_{\bar{Z}}$	|t|	P
Group I	15	5.73 mm. syst. 3.47 mm. diast.	± 4.102 ± 2.151	1.349 1.557	0.1 < P < 0.2 0.1 < P < 0.2

There is no significant difference between the changes.

Summary

Controls. In Group I non-smokers there was a significant fall (3.9 mm. Hg.) in diastolic blood-pressure; and in Group II there was a highly significant fall (6.6 mm. Hg.) in systolic pressure, and a probably significant fall (3.3 mm. Hg.) in diastolic pressure.

Cigarette-tests. In Group I smokers there was a significant rise (5.0 mm. Hg.)in systolic pressure.

Cigar-tests. In Group I (smokers and non-smokers) there was a significant rise (5.6 mm. Hg.) in systolic pressure; and in Group II there was a significant fall (3.6 mm. Hg.) in diastolic pressure.

Nicotine-tests I. There was no significant change in mean blood-pressure. A fall from 142 to 100 mm. Hg. in the systolic pressure was noted in one case, the diastolic remaining unchanged.

Nicotine-tests II. The mean blood-pressure showed no significant change. A rise in blood-pressure from 120/76 to 170/82 mm. Hg. was noted in one case.

In the *cigarette-tests* there was a significant average rise in systolic pressure of 5.8 mm. Hg. in Group I smokers and a probably significant rise in diastolic pressure in non-smokers over and above that in the controls.

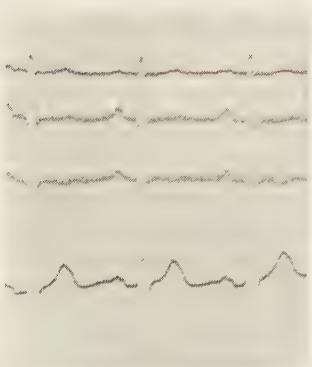
In the *cigar-tests* there was a significant average rise in systolic pressure of 10.1 mm. Hg. in Group I and 8.9 mm. Hg. in Group II over and above the systolic-pressure-rise in the controls.

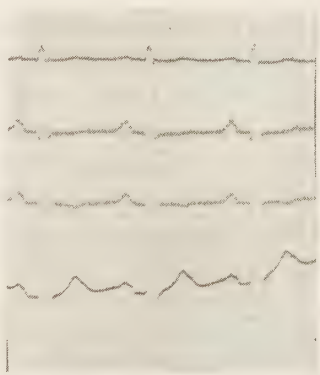
CHAPTER VIII

The Electrocardiogram on Tobacco-Smoking or after Injection of Nicotine during Hypoxia

The Normal Electrocardiographic Reaction during 17—18 Minutes' Hypoxia Breathing a CO_2-O_2-N_2 Mixture

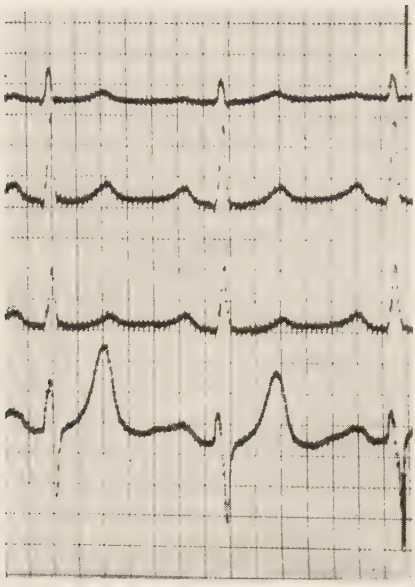
Inhalation of a gas mixture deficient in oxygen results in an increase in the heart rate with a simultaneous flattening of the T-waves. A progressive increase in the heart rate occurs as the oxygen saturation decreases. After breathing a CO_2-O_2 mixture for approximately 5 minutes the heart rate and the arterial oxygen saturation will have become stabilized, though a further change in heart rate by about 10 beats per minute or slightly more may occur in some persons. Spontaneous flattening of the T-waves occurs during the hypoxia test in spite of the fact that the oxygen saturation and heart rate are practically constant. This flattening, called here the 'time-factor', was least pronounced in Lead I and most pronounced in Leads CR_2 and CR_4. It may be considerable in some persons, as reported in a previous

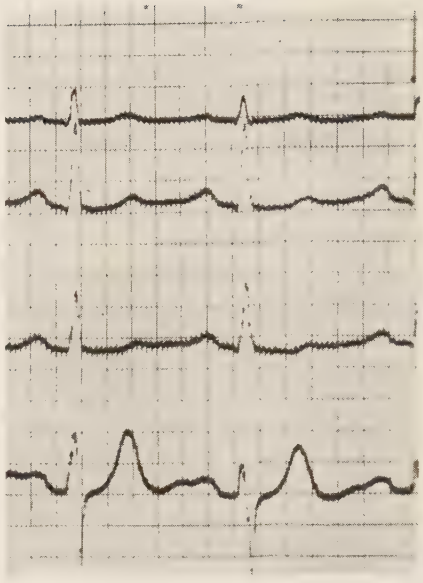




ECG no. 1. Subject no. 51. Medical student, aged 23 years, non-smoker. ECG after 6 minutes' hypoxia. Heart rate 90 beats per minute.

ECG no. 2. ECG after 17 minutes' hypoxia. Heart rate 90 beats per minute.





ECG no. 3. Subject no. 104. Male aged 38 years, non-smoker. ECG after 6 minutes' hypoxia. Heart rate 90 beats per minute.

ECG no. 4. ECG after 17 minutes' hypoxia. Heart rate 90 beats per minute. Flattening of all the T-waves, especially in Lead CR_4.

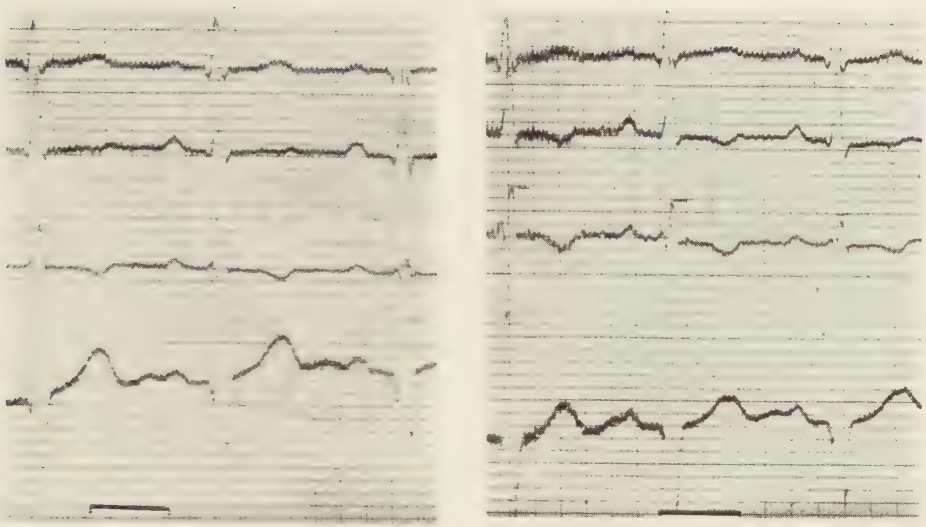
paper (von Ahn, 1954). Electrocardiograms nos. 1—4 illustrate the ECG during 17—18 minutes' hypoxia at rest (control test) in two subjects (nos. 51 and 104).

In case 51 the heart rate was constant during the whole test. There was no appreciable change in the height of the T-waves in Leads I—III, but in Lead CR_4 there was a slight flattening, and the time-factor was slight. In case 104 a marked flattening of all T-waves, especially in Lead CR_4, occurred, although the heart rate remained constant throughout the test; the time-factor was comparatively great.

The Electrocardiogram in the Smoking-tests

Illustrative cases

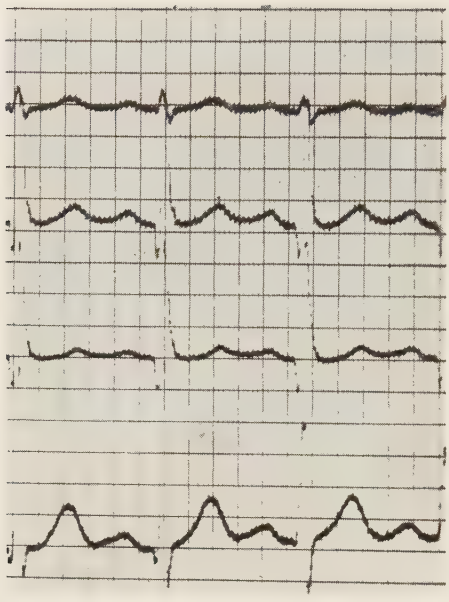
It appears from the electrocardiograms reproduced that smoking during hypoxia results in an increase in heart rate varying from 8 to 22 beats per minute, and flattening of the T-waves in these cases. In case 42 (ECG nos. 5—6) the heart rate increased by 8 beats per minute and T_2, positive-diphasic before smoking, became diphasic-negative after the smoking of one cigarette. T_3 became more deeply negative after smoking. In the control



ECG no. 5. Subject no. 42. Soldier, aged 20 years, healthy heart, non-smoker. ECG after 6 minutes' hypoxia and prior to smoking. Heart rate 84 beats per minute. T_2 alternates between diphasic and weakly positive. T_3 negative.

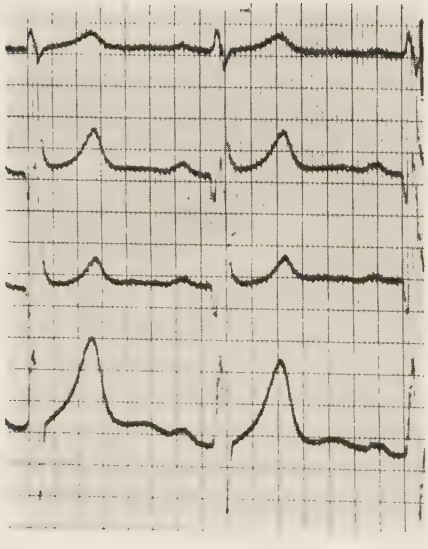
ECG no. 6. ECG after 17 minutes' hypoxia and after smoking a cigarette in 7—8 minutes. Heart rate 92 beats per minute. T_2 alternates between diphasic and negative. T_3 more deeply negative. T in CR_4 flattened.

test (without smoking) no similar change occurred after 17 minutes' hypoxia. In Cases 1 and 2 cigar-smoking during hypoxia produced an increase in heart rate by 22 and 14 beats per minute respectively (ECG nos. 13 14 and 7—8); on repeating the smoking-tests in the same way and using the same apparatus, but administering air instead of the gas mixture, the heart rate increased 28 and 13 beats per minute (ECG nos. 17—18 and 11—12). There was thus a similar increase in heart rate whether the smoking was carried out in room air or during hypoxia. The effect of cigarette- and cigar-smoking on the ECG is essentially the same. In some cases cigar-smoking exerts a more marked influence upon the ECG — naturally, since more nicotine is absorbed on the smoking of one gram of cigar tobacco than of the same amount of cigarette tobacco (= one cigarette). This is especially evident in subject no. 1 (ECG nos. 13 and 14): cigar-smoking resulted in a marked flattening of the T-waves, in particular in Lead CR_4 in which S-T was depressed as well, and an increase in the heart rate of 22 beats per minute. In the same subject (no. 1) an increase in heart rate by 34 beats per minute (from 88 – 122 beats/min.) occurred on cigarette-smoking. The T-wave in CR_4 became more markedly flattened after cigar-smoking, although the heart rate increased much more markedly

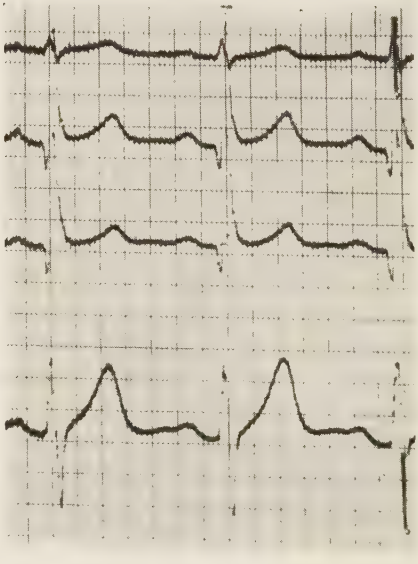


ECG no. 7

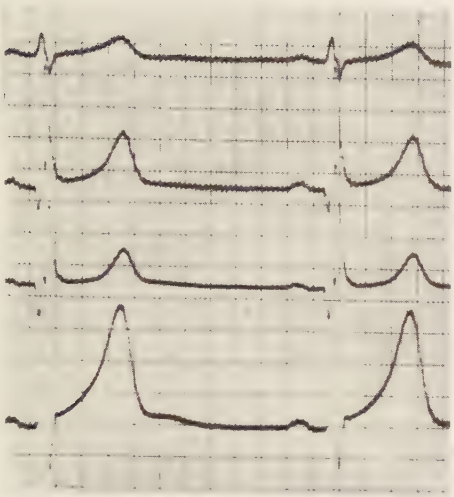
ECG no. 8



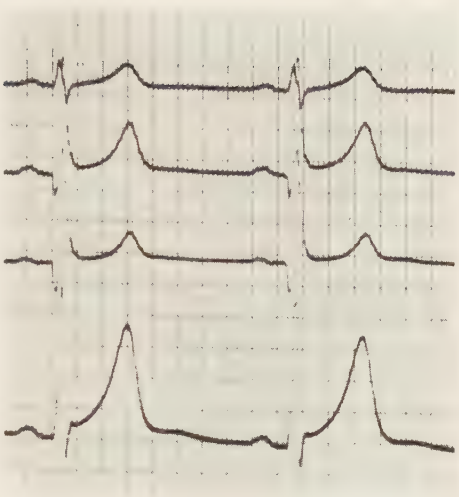
ECG no. 9



ECG no. 10



ECG no. 11



ECG no. 12

ECG no. 7. Subject no. 2. Medical student, aged 26 years. Healthy heart. Smoker. ECG after 6 minutes' hypoxia prior to smoking. Heart rate 106 beats per minute.

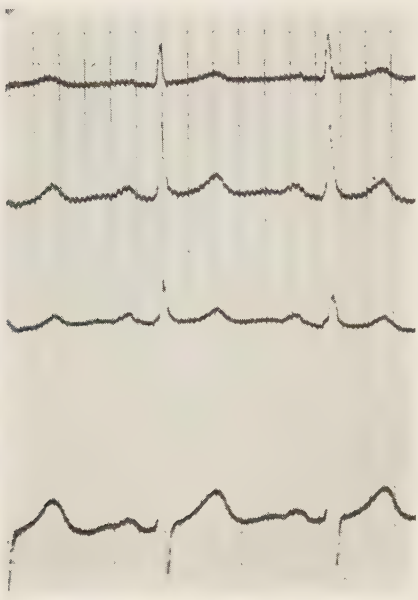
ECG no. 8. ECG after 17 minutes' hypoxia and after 8 minutes' cigar-smoking. Heart rate 120 beats per minute. Considerable flattening of the T-waves in Leads II, III and CR_4.

ECG no. 9. Subject no. 2. ECG 12 minutes after intravenous injection of 0.5 mg. dihydroergotamine (DHE 45) and after 6 minutes' hypoxia, prior to smoking of cigar. Heart rate 80 beats per minute.

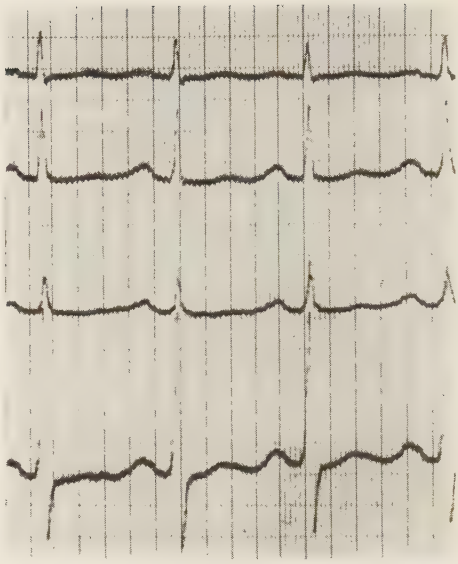
ECG no. 10. ECG after 17 minutes' hypoxia and after smoking cigar. Heart rate 90 beats per minute. Slight flattening of the T-waves.

ECG no. 11. Subject no. 2. Resting ECG prior to smoking. Heart rate 52 beats per minute.

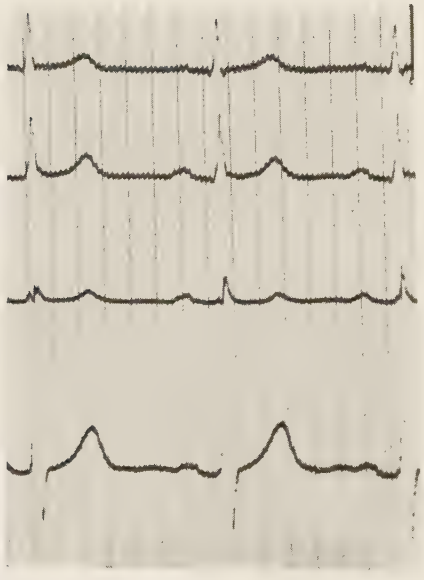
ECG no. 12. ECG after 8 minutes' cigar-smoking under normal conditions (no hypoxia). Heart rate 65 beats per minute. No substantial changes in the T-waves.



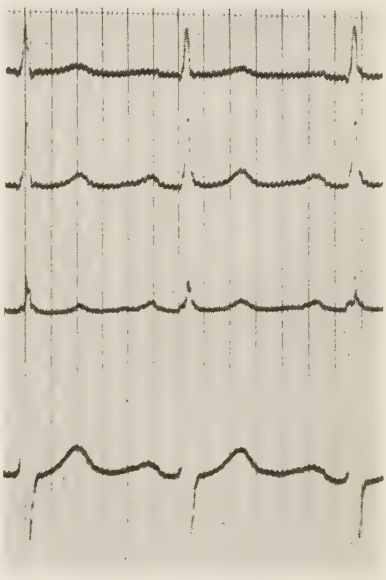
ECG no. 13



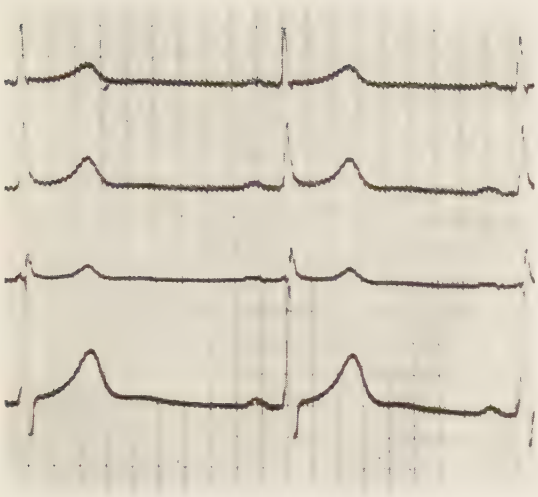
ECG no. 14



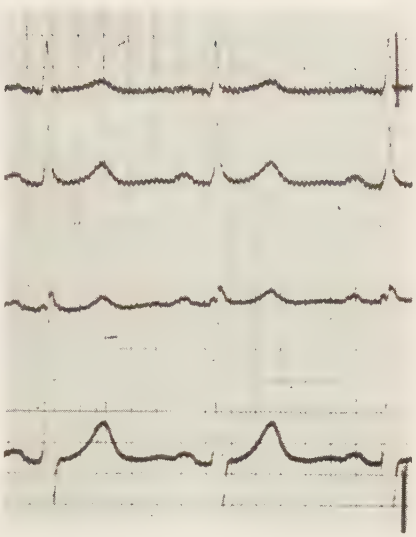
ECG no. 15



ECG no. 16



ECG no. 17



ECG no. 18

ECG no. 13. Subject no. 1. Medical student, aged 25 years. Healthy heart. Smoker. ECG after 6 minutes' hypoxia. Heart rate 93 beats per minute.

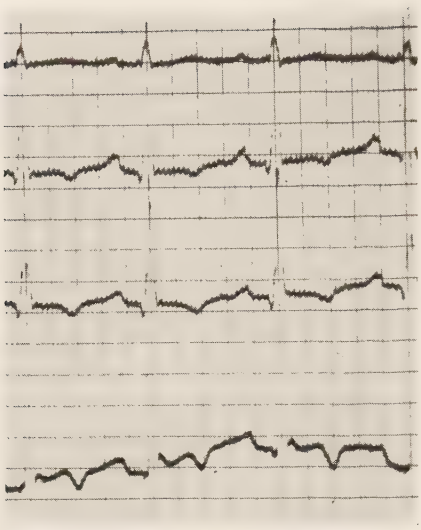
ECG no. 14. ECG after 17 minutes' hypoxia after smoking cigar. Heart rate 115 beats per minute. Marked flattening of all the T-waves. S-T depressed in all leads, especially in CR_4.

ECG no. 15. Subject no. 1. ECG 12 minutes after 1 mg. dihydroergotamine intravenously and after 6 minutes' hypoxia, prior to smoking. Heart rate 85 beats per minute.

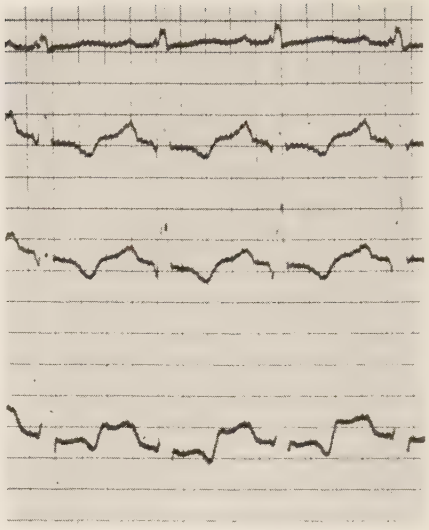
ECG no. 16. ECG after 17 minutes' hypoxia and after smoking cigar. Heart rate 95 beats per minute. Slight flattening of the T-waves.

ECG no. 17. Subject no. 1. Resting ECG prior to smoking. Heart rate 61 beats per minute

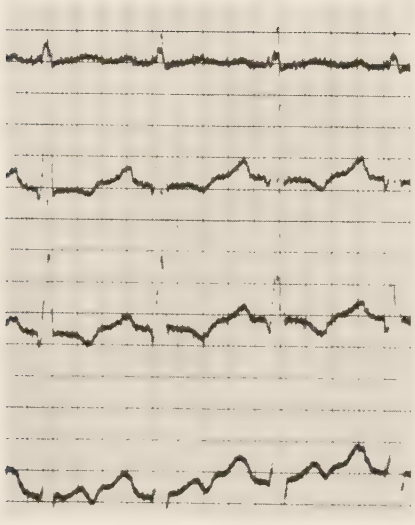
ECG no. 18. ECG after 8 minutes' cigar-smoking under normal conditions (no hypoxia). Heart rate 89 beats per minute. Slight flattening of the T-waves.



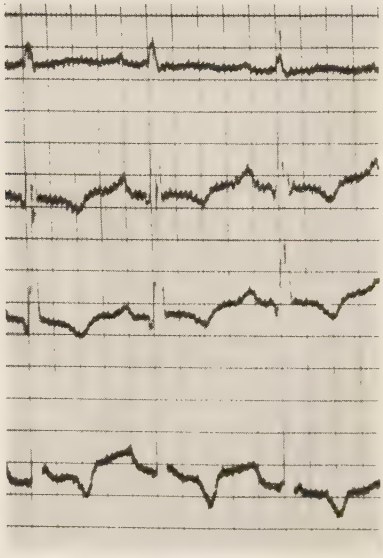
ECG no. 19



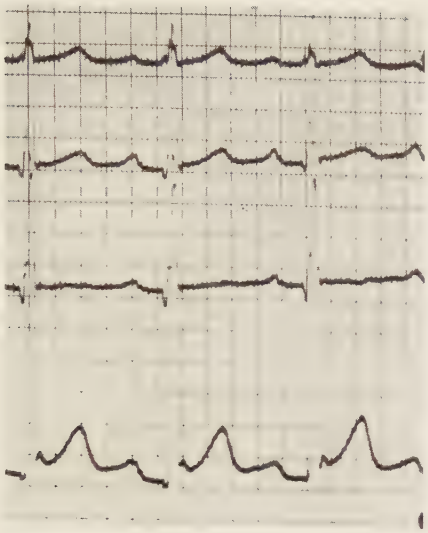
ECG no. 20



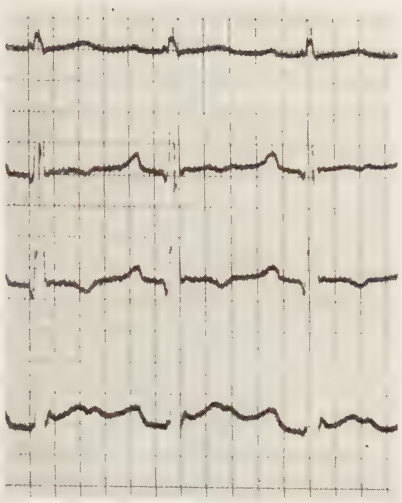
ECG no. 21



ECG no. 22



ECG no. 23



ECG no. 24

ECG no. 19. Subject no. 60. Soldier, aged 20 years. Possibly diseased heart. Non-smoker. Control test. ECG after 6 minutes' hypoxia. Heart rate 120 beats per minute. T-waves deeply negative in Leads II, III and CR_4.

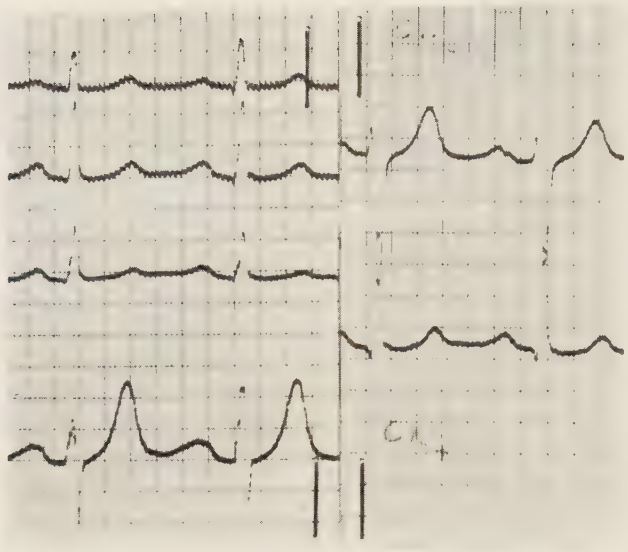
ECG no. 20. ECG after 17 minutes' hypoxia without smoking. Heart rate 120 beats per minute. T-waves somewhat more deeply negative.

ECG no. 21. ECG after 6 minutes' hypoxia. Heart rate 133 beats per minute. T-waves negative in Leads II, III and CR_4 as in the preceding test.

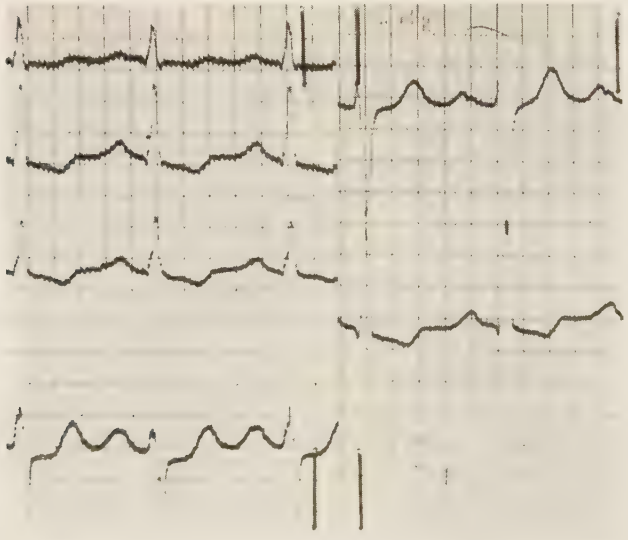
ECG no. 22. ECG after 17 minutes' hypoxia and after smoking cigar. Heart rate 130 beats per minute. T-waves somewhat more deeply negative (particularly in Lead CR_4) as in the control test.

ECG no. 23. ECG 20 minutes after intravenous injection of 0.5 mg. dihydroergotamine and after 6 minutes' hypoxia prior to smoking. Heart rate 105 beats per minute. T-waves now positive in Leads I, II and CR_4.

ECG no. 24. ECG after 17 minutes' hypoxia and after smoking cigar. Heart rate 110 beats per minute. The T-waves have now once again been changed pathologically: slight negative in Lead II, negative in Lead III and deformed and markedly flattened in Lead CR_4.



ECG no. 25. Subject no. 104. ECG after 6 minutes' hypoxia. Heart rate 90 beats per minute. Normal hypoxia ECG.



ECG no. 26. ECG after 17 minutes' hypoxia and after cigar smoking. Heart rate 114 beats per minute. T-waves diphatic in Leads II and CR_7, negative in Lead III, flattened in Lead CR_4. S-T depressed in all leads.

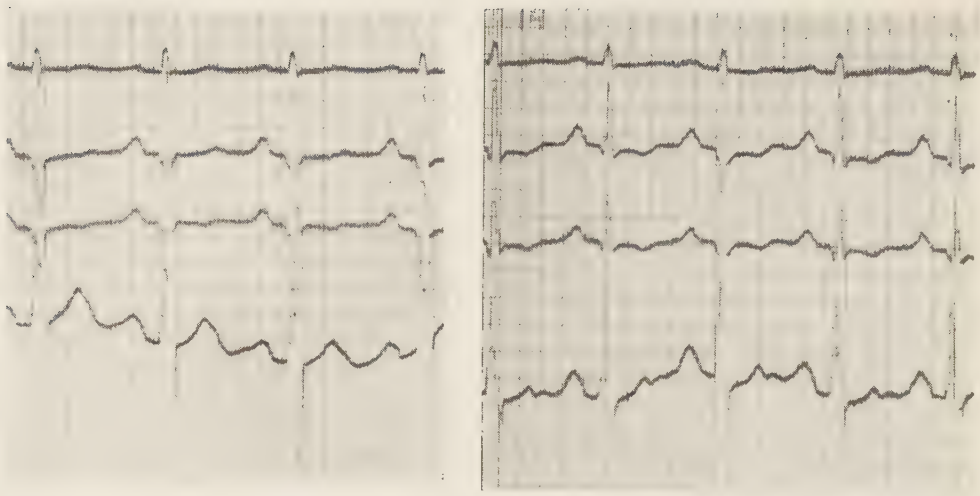
in the cigarette-test. The subject smoked 2—3 g. of tobacco. In subject no. 60, a soldier aged 20 years with a possible myocardial lesion, the T-waves became negative in Leads II, III, and CR_4 after 6 minutes' hypoxia. The changes were more pronounced after 17 minutes' hypoxia (ECG nos. 19—20). In this case the hypoxia test was considered to be pathological. The electrocardiogram after cigar-smoking and 17 minutes' hypoxia (ECG no. 22) showed no obvious change in comparison with the corresponding control ECG (ECG no. 20) — T in CR_4 became possibly slightly more negative after smoking.

As can be seen from ECG nos. 9—10 (Case 2) and 15—16 (Case 1) injection of dihydroergotamine (DHE 45) before the hypoxia test eliminated to a great extent the effect of smoking on the electrocardiogram. The counteracting effect of dihydroergotamine on nicotine is especially obvious in Case 1 (ECG nos. 13—16). Case 60 illustrates another observation concerning DHE 45 and nicotine. Following intravenous injection of 0.5 mg. of DHE 45 the electrocardiogram became normal after 6 minutes' hypoxia. During cigar-smoking the electrocardiogram once again showed 'pathological' changes (ECG nos. 23—24). These observations will be discussed at greater length in Chapter IX.

The older age group was considerably less affected than the younger during the smoking tests, as regards both heart rate and electrocardiogram (Chapter X). No appreciable ECG-changes occurred in the smoking-tests in Group II except in one case: in a healthy subject aged 38 years (Case 104) cigar-smoking produced 'pathological' ECG-changes (ECG nos. 3—4 and 25—26). The experiment was repeated twice with the same result.

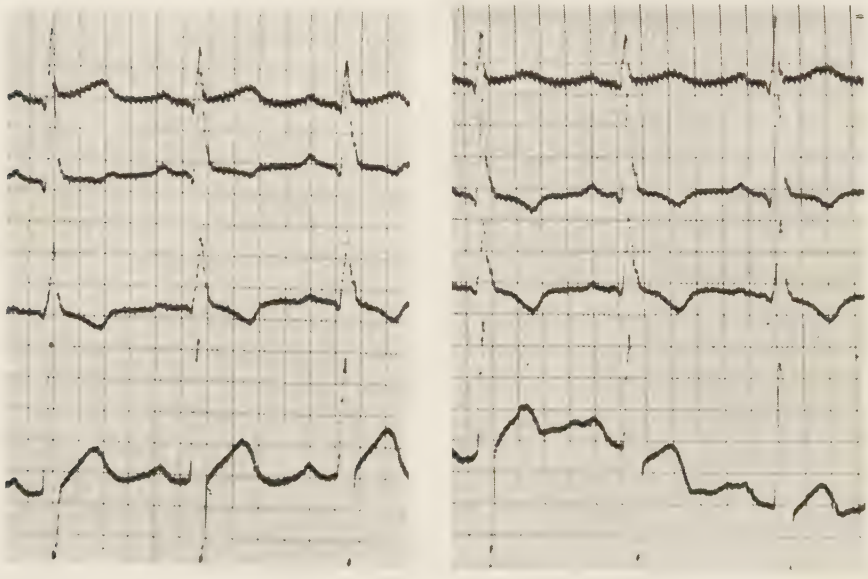
The Electrocardiogram after Injection of Nicotine

Intravenous injection of nicotine produces essentially the same ECG-changes as smoking. Only two cases are of special interest. Subject no. 51 was exceptionally susceptible to nicotine. The intended dose of 1 mg. could not be injected, but had to be reduced to 0.33 mg. The increase in heart rate ranged from 97 beats per minute after 6 minutes' hypoxia to 113 beats per minute after nicotine and 14 minutes' hypoxia. The electrocardiogram showed a marked change: T_2 and T_3 became diphasic and negative respectively; T in CR_4 became markedly flattened; S-T was depressed in all leads; and the P-waves increased considerably in height, especially in Leads II and CR_4 (ECG nos. 1—2 and 27—28). In Case 29, T_2 became negative and T_3 more deeply negative after injection of 3 mg. of nicotine, the heart rate remaining practically constant (ECG nos. 29—30); the dose of nicotine was well tolerated in this case.



ECG no. 27. Subject no. 51. ECG after 6 minutes' hypoxia before nicotine. Heart rate 97 beats per minute. Blood-pressure 142/76 mm. Hg.

ECG no. 28. ECG after 14 minutes' hypoxia, and after intravenous injection of 0.33 mg. nicotine. Heart rate 113 beats per minute. Blood-pressure 154/76 mm. Hg.



ECG no. 29. Subject no. 29. Soldier, aged 20 years. Smoker. ECG after 6 minutes' hypoxia. Heart rate 100 beats per minute. T_2 diphasic, T_3 negative.

ECG no. 30. ECG after 17 minutes' hypoxia and after intravenous injection of 3 mg. nicotine. Heart rate 104 beats per minute. T_1 flattened, T_2 negative, T_3 more deeply negative, T in CR_4 flattened.

Physiological saline was injected instead of nicotine in 15 cases. The electrocardiogram was unaffected.

The Heart Rhythm

Group I. In *the cigarette-tests* the rhythm remained regular in all cases but one, a smoker, in which a ventricular extrasystole was noted after smoking and 17 minutes' hypoxia. In *the cigar-tests* transient sinus arrhythmia occurred in one subject after 1 minute's smoking, but otherwise the rhythm was regular in all tests. In *the nicotine-tests* no arrhythmias were noted.

Group II. Only in one case were repeated supraventricular extrasystoles noted during the smoking-tests.

Arrhythmias were thus of rare occurrence during the smoking-tests. It is remarkable that no form of arrhythmia developed after injection of nicotine (Group I) during hypoxia, since the heart is then much more susceptible to nicotine than under ordinary circumstances (see Chapter V).

Signs and Symptoms

No untoward reactions occurred in Group I, either in *control-tests* or *smoking-tests,* to hinder the completion of the tests. Even the older age group tolerated well 20 minutes' hypoxia.

In *nicotine-tests I* four subjects complained of acroparaesthesiae, but only one (no. 51) developed severe reactions. He had palpitations and excessive hyperventilation just after the beginning of the injection, and complained of a general diffuse sensation of discomfort and anxiety. The palpitations continued throughout the test and the injection had to be stopped after 1½ minutes, when only 0.33 mg. of nicotine had been injected. The blood-pressure increased from 142/68 mm. to 154/76 mm. Hg. after the injection.

In *nicotine-tests II* most of the subjects tolerated well 3 mg. of nicotine injected intravenously over a period of 8 minutes. The effect of this amount of nicotine was in all cases more powerful than that of 1 mg. of nicotine. Two of the subjects developed signs of intoxication in the form of nausea and vomiting immediately after the test. In two cases the rate of injection had to be slowed down owing to severe hyperventilation and discomfort: the amount of nicotine injected was reduced to 1.44 and 1.85 mg. A third subject who received 3 mg. of nicotine developed excessive hyperventilation, which continued 2—3 minutes after the completion of the test; this subject developed tetany secondary to the hyperventilation, with pronounced spasm in the fingers. In a fourth case 3 mg. of nicotine produced moderate intoxica-

tion approximately 5 minutes after the test. The subject complained of weakness and fatigue, and had to go to bed. The day after the test he suffered from severe drowsiness. He had no cardiac symptoms, and no sickness or vomiting. The ECG showed no significant changes during the nicotine-test. In four other cases nicotine resulted in pronounced but transient euphoria. Six subjects developed acroparaesthesiae, two complained of anxiety, and five of severe weakness during or after the test. Severe intoxication occurred in none of the cases.

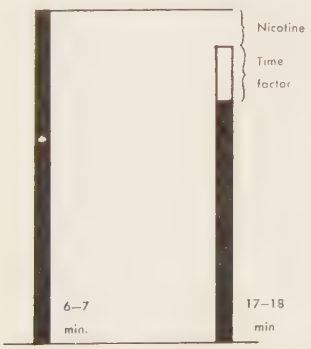
Summary

During a 17—18 minutes' hypoxia test breathing a CO_2-O_2 mixture a spontaneous flattening of the T-waves, called in this study the time-factor, occurs in spite of constant heart rate and constant oxygen saturation. This time-factor may be considerable in some individuals. Smoking during hypoxia results in a slight or moderate increase in the heart rate with a simultaneous flattening of the T-waves and a slight depression of the S-T segment. Intravenous injection of 1—3 mg. of nicotine produce essentially the same ECG-changes as smoking. Arrhythmias in the form of extrasystoles were rare in these smoking-tests, and no arrhythmias were noted in the nicotine-tests. Injection of nicotine during hypoxia results in increased hyperventilation, which may be considerable in susceptible individuals. Injection of 3 mg. of nicotine intravenously produces in some cases euphoria, in other cases moderate signs of intoxication.

CHAPTER IX

Discussion of the Origin of the Electrocardiographic Changes

The decrease in the amplitude of the T-waves which occurs on smoking during hypoxia is to a great extent due to the time factor. Even if this time factor is added to the height of the T-waves at 17—18 minutes' hypoxia there is still in most cases a difference in height between the T-waves as measured at 6—7 minutes' hypoxia (see the figure). This difference in height probably represents the effect of nicotine, which may be assumed to produce flattening of the T-waves by two different mechanisms. Firstly, nicotine may produce an increase in the heart rate with a '*physiological*' flattening of the T-waves through stimulation of the sympathetic ganglia. Secondly, it may cause by a nervous mechanism and through humoral agents a reduction in coronary flow to the extent that coronary insufficiency develops during the hypoxia test; this may result in *pathological* flattening of the T-waves. A sympatheticotonic reaction is released during the hypoxia test, which gives rise to an increase in the heart rate and a flattening of the T-waves (Cerletti and Kallenberger, 1948; Kiss and Slapak, 1951). On administration of tobacco-smoke or nicotine during the hypoxia test the heart rate increases even more, and the T-waves decrease further in height. The sympatheticotonic pattern of the electrocardiogram during hypoxia is thus accentuated after administration of nicotine. It has earlier been men-



The black columns indicate the amplitude of the T-waves at 6—7 min. hypoxia before smoking and at 17—18 min. hypoxia after smoking. The white column indicates the time factor.

tioned (Chapter III) that the ECG changes produced by smoking are evidence of an increased sympathetic tone of the heart. If this view is correct and applies also under conditions of hypoxia the ECG changes might be counteracted by vagomimetic drugs, and reproduced by sympatheticomimetic and vagolytic drugs or a physiological stimulus such as work.

Nicotine and Dihydroergotamine (DHE 45)

Vagomimetic agents such as prostigmine (Ask-Upmark, 1941) and ergotamine (Nordenfelt, 1941) result in reduction of the heart rate and increase in the height of the T-waves. According to Nordenfelt, the ECG changes produced by ergotamine have the following appearance: slow sinus rhythm, low P-waves especially in Leads II and III, higher and wider T-waves than usual, and not rarely an elevation of the S-T segment. When the sympathetic tone is increased the ECG shows opposite changes, as has been mentioned in Chapter IV. According to Rothlin and Cerletti (1950), the ergot alkaloids produce active vagal tone released via the central nervous system. In this way an extrinsic change in cardiac tone in a vagotonic direction develops. In addition, the ergot alkaloids are considered to exert an indirect, extrinsic adreno-sympatheticolytic effect, to which the heart however is refractory in therapeutic doses.

It has been seen in cases 1 and 2 that the ECG changes provoked by smoking are considerably less marked if dihydroergotamine is administered prior to the hypoxia test: this agent thus counteracts the effect of nicotine (ECG nos. 9—10 and 15—16). In case 60, the 20-year-old soldier with a pathological hypoxia test, the ECG at 6 minutes' hypoxia became normal after intravenous injection of 0.5 mg. of dihydroergotamine. It is now a well-known fact that the ergot alkaloids can restore to normal ECG changes of organic origin as well (Scherf and Schlachman, 1948; Kiss and Slapak, 1951). After intensive cigar-smoking for only one minute the T-waves showed significant flattening in Leads I and CR_4, and they became isoelectric in Lead II and negative in Lead III; the ECG showed a gradually progressive pathological change during the test, and after 8 minutes' smoking had the pattern of ECG no. 24: the effect of nicotine was in this case more potent than the vagotonic effect of dihydroergotamine. In addition to possible myocardial damage this subject suffered from neurocirculatory asthenia, and it is possible that this functional state was reflected in the ECG as increased sympathetic tone which was eliminated by dihydroergotamine and returned when the subject smoked. The subject had no disability before or after the smoking test. It is unlikely that these ECG changes provoked by smoking were of coronary origin. In case 104 cigar-smoking also resulted in 'pathological' ECG changes, despite the fact that the subject

received 0.6 mg. of dihydroergotamine intramuscularly 30 minutes before the hypoxia test. In a new experiment 'pathological' ECG changes were produced in the same case by 4–5 minutes' cigar-smoking, after which 1 ml. of Hydergin (CCK 179) was injected intravenously without effect on the ECG changes. The subject was a healthy man aged 38 years with good physical efficiency. The ECG on ordinary exercise and the X-ray of the heart were normal (heart volume 395 ml. per square metre body surface, heart configuration normal). He suffered no discomfort from the experiments, and it is very unlikely that the ECG changes provoked by smoking were due to coronary insufficiency. It is probable that here too nicotine (perhaps by stimulating the secretion of adrenaline) produced such powerful sympathetic stimulation that this predominated in spite of the vagotonic effect of dihydroergotamine.

Summary

Dihydroergotamine can in certain cases almost completely prevent the development of the ECG changes provoked by smoking. On the other hand heavy smoking may change a vagotonic ECG in a sympatheticotonic direction. There is thus a reciprocity between dihydroergotamine and nicotine with regard to the effect on the electrocardiogram. This supports the view that electrocardiographic changes associated with smoking are due to increased sympathetic tone.

Nicotine and Adrenaline

Since nicotine is capable of liberating adrenaline from the suprarenals it may be justifiable to touch briefly upon the effect of adrenaline on the heart and the electrocardiogram. Adrenaline is produced not only in the suprarenal glands but also in the heart muscle itself (Raab, 1941; Raab and Soule, 1944; von Euler, 1952) and by the sympathetic neurones in the arterial walls (Raab, 1941) under the influence of sympathetic stimuli. Adrenaline exerts a highly stimulant effect on the myocardium, and increases the work of the heart, the cardiac metabolism, and vigorously the oxygen consumption. Formerly it was held that adrenaline had a direct dilator effect on the coronary vessels (Morawitz and Zahn, 1914; Rössler, 1930), but this opinion has since been modified. Adrenaline is now considered to dilate the coronary vessels only indirectly, by powerful stimulation of the myocardial metabolism, with the production of vasodilator metabolites (Gregg, 1950; Melville and Lu, 1950; Folkow, 1953): the coronary vessels are thus dilated but the increased coronary flow does not nearly correspond to the sudden increase in oxygen consumption (Gollwitzer-Meier, 1939). The oxygen

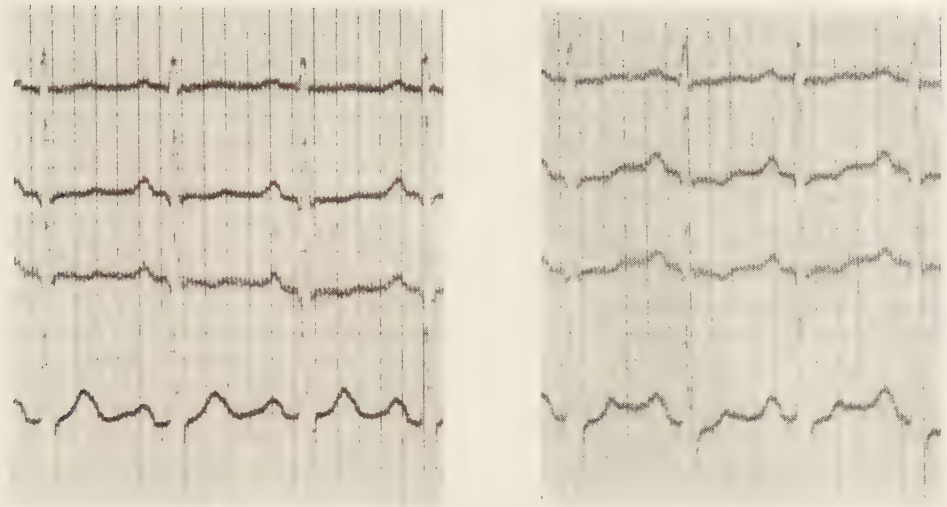
requirement of the heart is increased by nearly 50% when stimulated by such small quantities as 1—2 γ of adrenaline, and 3½ times by 10 γ of adrenaline. Such a sudden increase in oxygen consumption without sufficiently increased oxygen supply may result in myocardial hypoxia (Gollwitzer-Meier, 1939; Raab, 1941; Raab and Soule, 1944; Gregg, 1950; Raab, 1953). This explains why adrenaline may precipitate angina pectoris in patients with coronary disease and, in large doses, also in healthy persons (Nordenfelt, 1941; Raab, 1944). Nordenfelt found obvious coronary insufficiency in a woman aged 34 years with a clinical healthy heart, in whom 0.25 mg. of adrenaline was injected intravenously by mistake; S-T in Leads I and II were considerably elevated, as in acute heart infarction.

It may be questioned whether tobacco-smoking or injection of nicotine in the doses employed (1—3 mg.) may result in appreciably increased secretion of adrenaline. If this is the case, then tobacco-smoking should predispose to angina pectoris in patients with coronary disease. According to Short and Johnson (1939), adrenaline (1 mg. subcutaneously) and tobacco-smoking have similar effects on pulse, blood-pressure, skin temperature, and blood sugar; this they explain by the fact that both these agents stimulate the sympathetic nervous system — adrenaline the nerve endings and nicotine the ganglia.

Three tests were performed with injection of adrenaline during hypoxia. In the first case (subject no. 51), in which intravenous injection of nicotine (0.33 mg.) resulted in an exceptionally quick and marked reaction (Chapter VIII), adrenaline was also injected intravenously in very dilute solution. 7.5 γ of adrenaline was administered over a period of 45 seconds. About 30 seconds after the beginning of the injection the subject developed severe hyperventilation and a general feeling of discomfort but no cardiac symptoms. The blood-pressure was 150/70 mm. before and 140/80 mm. Hg. after the injection. The heart rate increased from 100 beats per minute before to 110 5 minutes after the injection (ECG nos. 31—32).

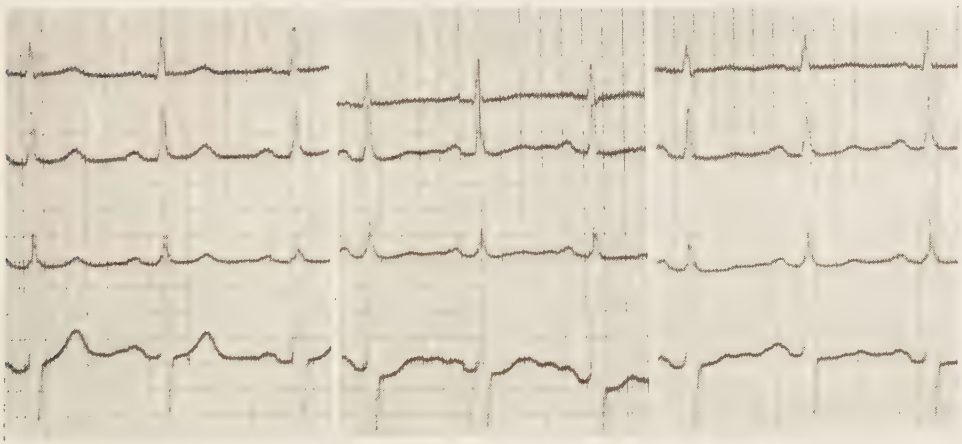
The electrocardiogram recorded after adrenaline shows great similarity in pattern to that recorded after nicotine (ECG nos. 27—28). As appears from Diagram 3 (page 69) the T-waves in Lead CR_4 show the same degree of flattening after adrenaline as after nicotine. The heart rate showed a similar increase in both tests.

In the second case (subject no. 1), 30 γ of adrenaline was injected intravenously between the 9th and 12th minutes of the hypoxia test. The subject developed moderate hyperventilation but no cardiac symptoms. The blood-pressure was 135/80 mm. before the injection, 150/78 mm. 1 minute after, and 135/75 mm. Hg. 5 minutes after. The heart rate increased from 97 to 110 beats per minute after the injection, and was 100 beats per minute 5 minutes later (ECG nos. 33—35).



ECG no. 31. Subject no. 51. ECG after 6 minutes' hypoxia, before adrenaline. Heart rate 100 beats per minute. Blood-pressure 150/70 mm. Hg.

ECG no. 32. ECG after 15 minutes' hypoxia and 5 minutes after intravenous injection of 7.5 γ adrenaline. Heart rate 110 beats per minute. Blood-pressure 145/80 mm. Hg.



ECG no. 33. Subject no. 1. ECG after 6 minutes' hypoxia, before adrenaline. Heart rate 97 beats per minute. Blood-pressure 135/80 mm. Hg.

ECG no. 34. ECG after 12 minutes' hypoxia and immediately after intravenous injection of 30 γ adrenaline. Heart rate 110 beats per minute. Blood-pressure 150/78 mm. Hg.

ECG no. 35. ECG after 17 minutes' hypoxia, and 5 minutes after the end of the injection. Heart rate 100 beats per minute. Blood-pressure 135/75 mm. Hg.

The T-waves show a sudden flattening after adrenaline, in spite of little or no increase in heart rate. Diagram 4 (page 69) shows a comparison between the flattening in the T-waves after adrenaline, cigar-smoking, and nicotine. In the third case (subject no. 50), 17.5 γ of adrenaline was injected intravenously over a period of 3 minutes. The subject had slight palpitations and slightly increased hyperventilation, but otherwise no discomfort. The blood-pressure changed from 140/70 mm. to 150/60 mm. 2 minutes after the injection, and was 145/65 mm. Hg. 5 minutes after the injection. The heart rate increased from 92 to 100 beats per minute immediately after the injection, and then remained constant throughout the test. As after adrenaline in the second case the T-waves showed a sudden flattening; but on the other hand after intravenous injection of 1 mg. of nicotine the flattening of the T-waves was only moderate.

It is difficult to produce pure sympathetic stimulation in man by means of adrenaline, owing to the fact that the simultaneous increase in the blood-pressure which occurs releases reflex stimulation of the vagus. The systolic blood-pressure increased in two of the cases by only 15 mm., however, i.e. about as much as in smoking. In the first case (no. 51) nicotine and adrenaline produced similar ECG changes of sympatheticotonic type. In the two other cases, however, adrenaline exerted a much more potent effect on the ECG than did nicotine. It is possible that the sudden flattening of the T-waves after adrenaline in these two cases was due to the anoxiating effect of adrenaline, which is probably particularly deleterious to a heart already subject to hypoxia. In the second case (subject no. 1) the ECG recorded after cigar-smoking is somewhat similar to that after adrenaline (cf. ECGs nos. 13—14 and 33—35). In subjects nos. 60 and 104, too, marked ECG changes occurred after heavy cigar-smoking. In these two cases it is reasonable to assume that cigar-smoking had caused increased secretion of adrenaline with marked ECG changes as a result: in case 60 little or no increase in heart rate was noted on smoking, in spite of pronounced flattening of the T-waves — a typical effect of adrenaline (Sjöstrand, 1951). The ECG changes observed in case 29 after injection of 3 mg. of nicotine may also be explained in this way (ECG nos. 29—30).

Summary

Three experiments were performed with injection of adrenaline during hypoxia. In one case intravenous adrenaline (7.5 γ) produced practically the same ECG changes as 0.33 mg. of nicotine, viz. an ECG of sympatheticotonic pattern. In the other two cases adrenaline (17—30 γ) produced a sudden flattening of the T-waves of a type quite different from that seen after smoking or injection of nicotine; in these two cases it is possible that

adrenaline through its anoxiating effect precipitated a certain degree of coronary insufficiency. The 'pathological' ECG changes provoked by heavy smoking are probably due to increased secretion of adrenaline.

Nicotine and Atropine

If it is so that the T-waves are flattened by nicotine simply by way of an increase in heart rate, then it should be possible to produce the same effect by means of some other drug which also increases the heart rate without considerably influencing the coronary circulation. Since there is no drug which quickens the heart rate without otherwise influencing the cardiovascular system experiments were performed giving small doses of atropine during hypoxia. Atropine speeds up the heart rate by blocking the vagus. The aim was to give atropine in a dose enough to increase the heart rate about as much as did smoking and nicotine. In one instance (subject no. 2) 0.35 mg. of atropine was injected intravenously without effect on the heart rate, whereas in two other cases 0.75 mg. (subject no. 18) and 1 mg. (subject no. 56) of atropine had the desired effect.

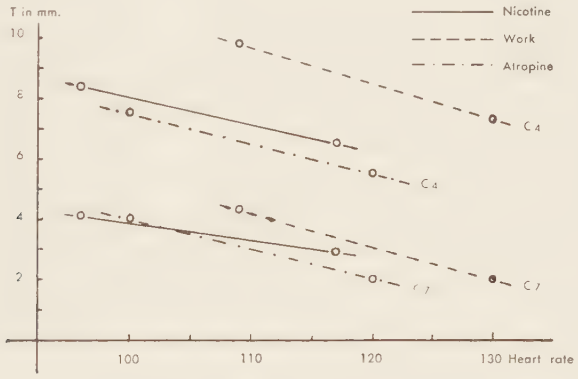


Diagram 1.

Subject no. 18. Comparison of the T-waves after atropine (0.75 mg.), nicotine (1 mg.), and exercise (total 750 kgm.), during hypoxia. The lines drawn between the amplitudes of the T-waves at 6 and 17 minutes' hypoxia have the same inclination in Leads CR_4 and CR_7 in all tests.

As can be seen, the flattening of the T-waves during hypoxia in this case is the same whichever means was used to increase the heart rate. In the third case (subject no. 56) the flattening of the T-waves was slightly less marked in Leads CR_2 and CR_4 after the smoking of one cigarette than after atropine, but in Lead CR_7 the degree of flattening was the same.

The relationship between nicotine and exercise will be discussed under the next heading.

Exercise Tolerance Tests by means of the Bicycle Ergometer

As appears from the above, smoking and injection of nicotine result in an increase in heart rate with a slight or moderate flattening of the T-waves. Adrenaline however produces a marked flattening of the T-waves even without appreciable increase in heart rate. It may be questioned whether the flattening of the T-waves which occurs after smoking and nicotine is more or less pronounced than or equal to that which occurs on physiological increase in heart rate. Physical exercise on the bicycle ergometer was chosen as a 'physiological' means of increasing the heart rate during hypoxia. The oxygen supply of the heart is considerably reduced during the hypoxia test, but coronary insufficiency need not necessarily develop on that account. It is probable that owing to compensating factors the myocardium in young healthy persons is supplied with enough oxygen when the work done is moderate. In the exercise tests the aim was to adjust the amount of work so that the heart rate increased about as much as on smoking, without signs of insufficiency appearing: the average work was 80 kgm. per minute for 8 minutes (Chapter VI). The exercise tolerance test was performed in a recumbent position, and under exactly the same conditions as in the smoking and nicotine tests. Two of the subjects developed considerable hyperventilation during the test - the amount of work was in these cases relatively high, total 1240 kgm. and 1028 kgm. respectively; the other subjects suffered no appreciable discomfort during the exercise test. 'Pathological' ECG changes occurred in none of the cases.

The diagrams below demonstrate the correlation between the T-waves in nicotine and exercise tests. Lines are drawn between the amplitudes of the T-waves at 6 and 17 minutes' hypoxia before and after the stimulus. The T-waves are dotted in in relation to the heart rate.

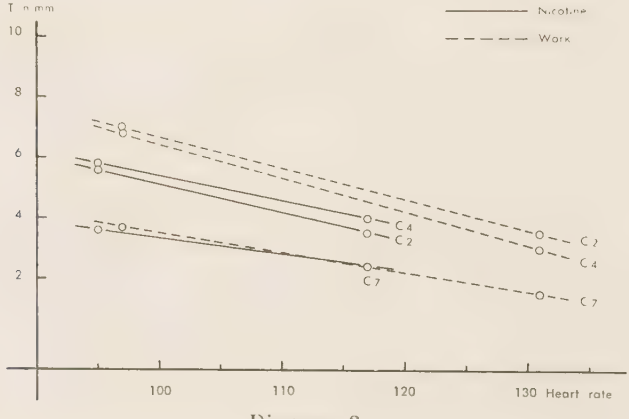


Diagram 2.

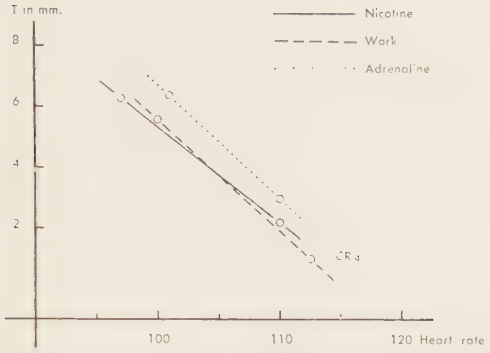


Diagram 3.

Subject no. 51. The straight lines demonstrate the flattening of the T-waves in Lead CR_4 after nicotine (0.33 mg.), adrenaline (7.5 γ), and exercise (926 kgm.). All three lines have the same inclination, indicating that the electrocardiogram was equally influenced in each of the three tests.

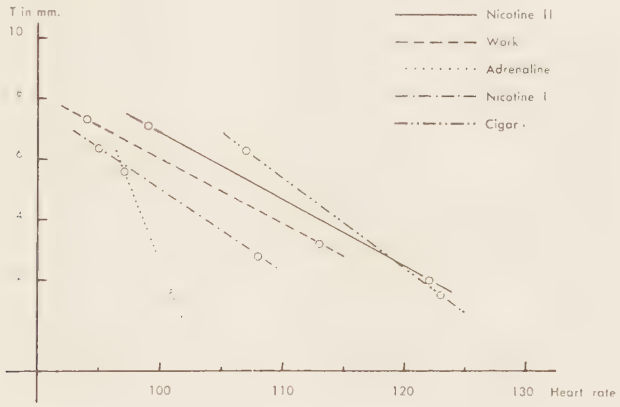


Diagram 4.

Subject no. 1. Comparison between the flattening of the T-waves in Lead CR_4 after cigar-smoking, nicotine (1 mg. and 3 mg.), adrenaline (30 γ), and exercise (520 kgm.). The lines have practically the same inclination except for that of adrenaline which inclines steeply. Thus adrenaline (in the dose employed) exerts a considerably more potent effect on the T-waves than do nicotine and exercise.

Diagram 2.

Subject no. 3. The straight lines demonstrate the flattening of the T-waves in Leads CR_2, CR_4, and CR_7 after exercise and intravenous injection of 3 mg. of nicotine. The nicotine line has exactly the same inclination as the 'physiological' line after exercise in the various leads.

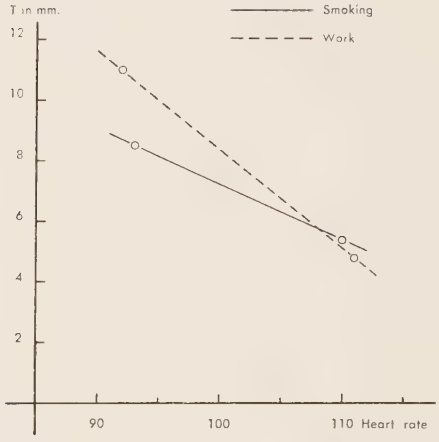


Diagram 5.

Subject no. 104. Comparison between the T-waves in Lead CR_2 after cigar-smoking and exercise (372 kgm.). The T-waves are somewhat less flattened in the cigar-test than in the exercise test.

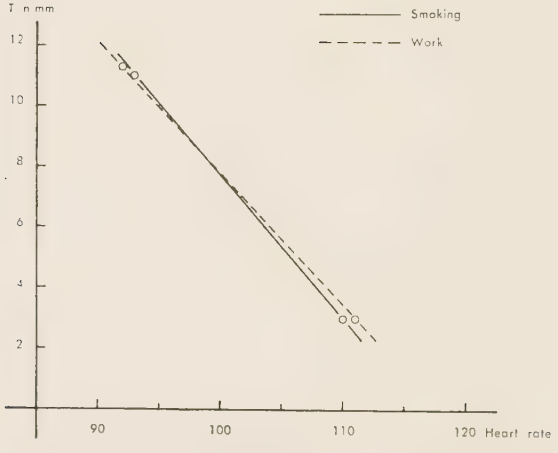


Diagram 6.

Subject no. 104. Comparison between the T-waves in Lead CR_4 after cigar-smoking and exercise. The T-waves are flattened to the same extent in both tests.

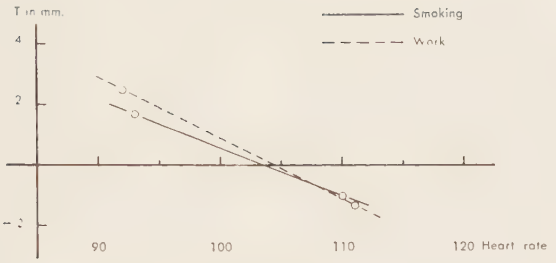


Diagram 7.

Subject no. 104. Comparison between the T-waves in Lead CR_7 after cigar-smoking and exercise. The T-waves are flattened to the same extent in both tests.

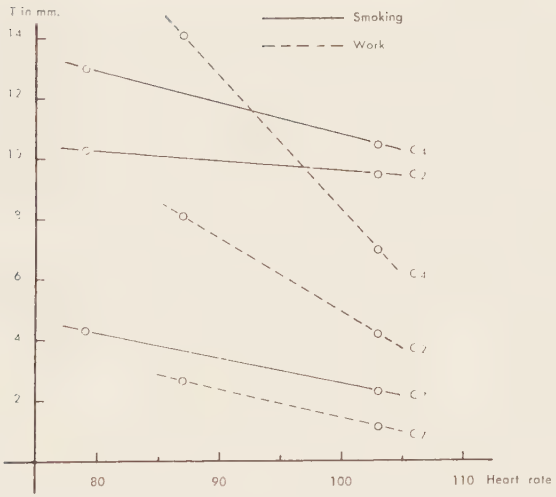
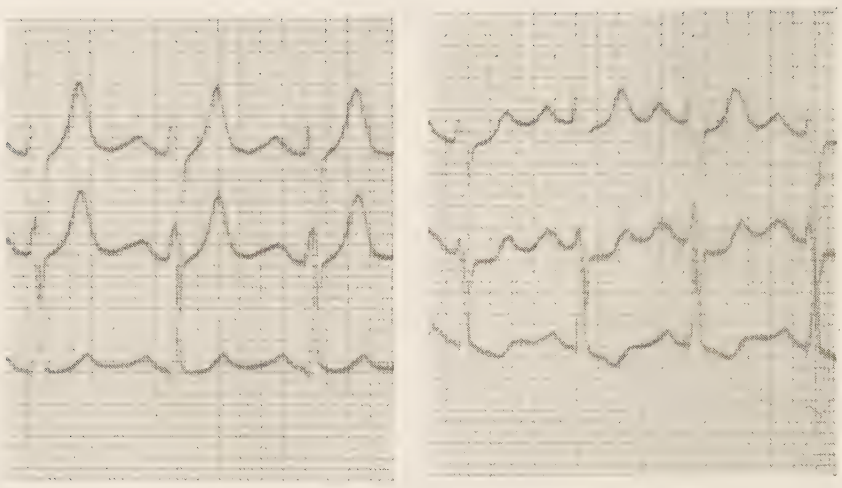


Diagram 8.

Subject no. 56. Comparison between the flattening of the T-waves in Leads CR_2, CR_4, and CR_7 after the smoking of one cigarette and after exercise (total 500 kgm.). The lines are similarly inclined in Lead CR_7, but show considerably less marked inclination after smoking than after exercise in Leads CR_2 and CR_4.



ECG no. 36. Subject no. 104. ECG after 6 minutes' hypoxia before work. Heart rate 90 beats per minute. Blood-pressure 142/80 mm. Hg. Leads CR_2, CR_4, CR_7.

ECG no. 37. ECG after 17 minutes' hypoxia, and work (372 kgm.). Heart rate 110 beats per minute. Blood-pressure 155/72 mm. Hg. Compare with ECG no. 26 after cigar-smoking.

In subject no. 104 (Diagrams 5–7) in whom cigar-smoking produced 'pathological' ECG changes, light work had the same effect on the ECG (ECGs nos. 36—37). May an ECG showing the same changes after smoking or injection of nicotine as after a physiological stimulus (work) in a person with a clinically normal heart be interpreted as pathological? This is only justifiable if it is reasonable to suppose that the work also precipitated coronary insufficiency. The work performed in these tests (except possibly in two cases) may be regarded as light, even though it was carried out under hypoxia, and it is unlikely that it resulted in clinical coronary insufficiency. Nicotine must produce a more pronounced ECG-reaction than does physical work if the reaction to it is to be designated as pathological.

Summary

In half the cases the flattening of the T-waves after nicotine was practically equal to that after exercise; in the other half a more marked decrease in the height of the T-waves occurred after exercise than generally after nicotine. This will be discussed at greater length in the next chapter.

CHAPTER X

Further Discussion on the Origin of the ECG Changes

Statistical Analysis of the Electrocardiographic Findings

As has been seen in the foregoing chapters, simultaneous flattening of the T-waves and increase in heart rate occur during the smoking and nicotine tests under hypoxia. The chief problem for the statistical analysis was,

Has nicotine any influence on the ECG over and above its effect of increasing the heart rate? The problem is complicated, however, by the fact that a depression of the T-waves independent of the heart rate — here called the 'time factor' — was noted in the controls (see Chapter IX). The time factor is a result of the extended hypoxia. As the effect of nicotine on the T-waves via the heart rate, it must be eliminated before an evaluation can be made of any residual effect of nicotine. We had thus to introduce a variable which would at one and the same time eliminate the time factor and the effect of quickening of the heart rate on the T-waves. It may be questioned whether the time factor is the same in the smoking and nicotine tests as in the controls; in other words, 'Is the time factor constant even though the heart rate may change?' If we correct the flattening of the T-waves after smoking and nicotine firstly with regard to the time factor and secondly with regard to the heart rate we must assume that the time factor is independent of changes in heart rate. The time factor can be eliminated according to the formula,

$$(S'' - S')_i - (C'' - C')_i$$

in which

S'' is the amplitude of the T-wave in mm. after smoking and 17 minutes' hypoxia;

S' is the amplitude of the T-wave after 6 minutes' hypoxia but before smoking;

C'' and C' are the amplitudes of the T-waves in the controls at 17 and 6 minutes' hypoxia respectively;

i represents the i^{th} individual.

To correct the T-waves for changes in heart rate the following formula can be used.

$$(S'' - S')_i - b\,(Fr_{s''} - Fr_{s'})_i$$

Here

b indicates the regression coefficient of the relationship between the changes in the amplitude of the T-waves and the changes in heart rate;

$Fr_{s''}$ is the heart rate in beats per minute after smoking and 17 minutes' hypoxia;

$Fr_{s'}$ is the heart rate after 6 minutes' hypoxia but before smoking.

If the changes in heart rate (Δ Fr) are dotted in along the abscissa, and changes in the amplitude of the T-wave (Δ T) along the ordinate, the line of regression is obtained (see Fig. 1). The inclination of the line (b) thus indicates the relationship between the changes in the amplitude of the T-wave and changes in heart rate.

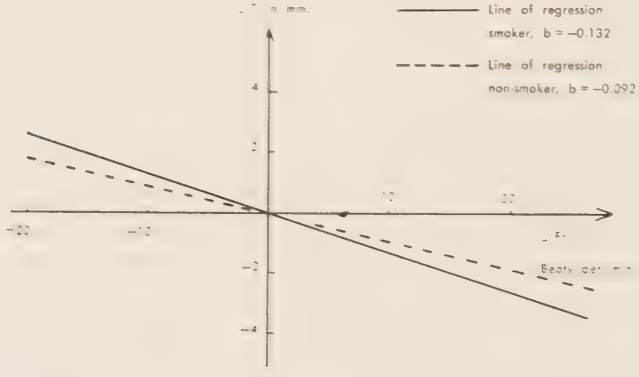


Fig. 1.

The problem now was to find the physiological relationship between the changes in the amplitude of the T-wave and the changes in heart rate under the given experimental conditions, viz. during hypoxia. This function is linear under ordinary conditions (Sjöstrand, 1950), *but is it also linear during hypoxia?* In some of the exercise tolerance tests under hypoxia in which there was successive increase in heart rate, this was investigated particularly. It was found that in these cases too the T-wave decreased linearly in height with increasing heart rate. (see Fig. 2).

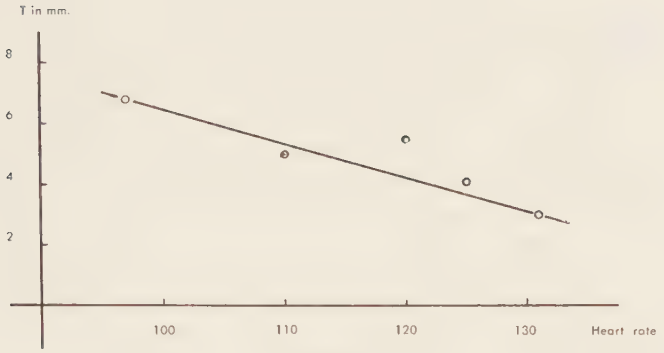


Fig. 2.

Fig. 2 shows the same regression line on exercise during hypoxia as that in Diagram 2, Chapter IX. Three additional points (T-waves) are plotted to demonstrate the linearity of the curve.

It was thus necessary to establish in what way the amplitude of the T-wave changes when the heart rate is quickened by means of a physiological stimulus under hypoxia. By the method used (bicycle ergometer) it was possible to obtain technically acceptable electrocardiograms in the chest leads only, and for this reason an additional procedure was necessary in order to be able to correct the changes in the amplitude of the T-waves in the standard limb leads. In the various tests on the same individual the heart rate has shown different values at 6 minutes' hypoxia. These variations in heart rate thus reflect the spontaneous individual variations from day to day. The variation in heart rate in the 6 minutes' hypoxia tests (Group I) ranged from — 36 to + 18 beats per minute. If these changes in heart rate are correlated with the corresponding changes in the amplitude of the T-waves a relationship between these variables can be established. If correction is made by means of a regression coefficient calculated in this way, then this will imply the presumption that this coefficient would be equal under a given experimental condition in which the heart rate is changed by means of a given stimulus.

On the basis of the two above assumptions the T-waves can be corrected for both time factor and heart rate according to the following formula,

$$X_i = (S'' - S')_i - (C'' - C')_i - b\,[(Fr_{s''} - Fr_{s'})_i - (Fr_{c''} - Fr_{c'})_i]$$

in which

X_i indicates the effect of nicotine on the i^{th} individual;

b is calculated from the spontaneous individual variations at 6 minutes' hypoxia;

Fr indicates the heart rate in smoking-tests and controls.

This method is designated *Alternative I.*

As this method of correction is based on two unproved assumptions an additional method has been used — *Alternative II.* In this way it is possible directly to compare the flattening of the T-waves after exercise (bicycle ergometer) and nicotine, both of which produce increase in heart rate. Here the time factor may be disregarded. The procedure is illustrated by the formula,

$$X_i = (S'' - S') - [a + b\,(Fr_{s''} - Fr_{s'})]$$

in which

X_i is the difference between the amplitudes of the T-waves after nicotine and exercise;

a indicates the point where the exercise line is cut off on the ordinate;

b is the regression coefficient of the relationship ΔT and ΔFr (see Fig. 3).

$Fr_{s''}$ and $Fr_{s'}$ indicate, as before, the heart rate after and before smoking and injection of nicotine.

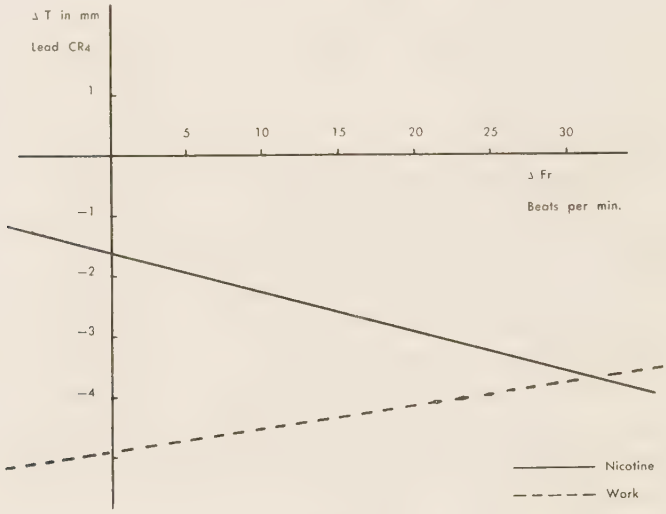


Fig. 3.

(The region of dots was reduced to a line according to the method of least squares, viz. $\Delta T = a + b\Delta Fr$.)

A considerably more marked spontaneous change in heart rate was noted in the controls of Group II than in those of Group I. In Group II it was possible to note the combined effect of hypoxia and the change in heart rate in a particular experimental situation. From this a relationship between the

changes in the amplitudes of the T-waves and the changes in heart rate can be calculated: the function is expressed by the formula $\Delta T = a + b \Delta Fr$. (See Fig. 4.)

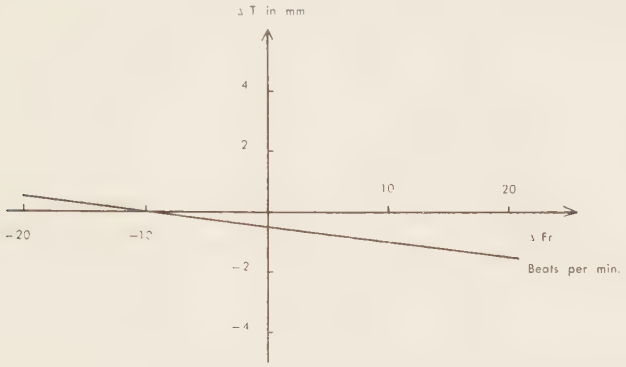


Fig. 4. The above given line of regression demonstrates the relationship between the changes in heart rate and the changes in the amplitude of the T-wave (Lead CR_7). $a = -0.490$, $b = -0.050$.

Our method of correction, called *Alternative III,* is

$$X_i = (S'' - S') - [a + b\,(Fr_{s''} - Fr_{s'})]$$

in which

X_i is the effect of nicotine on the electrocardiogram;

S'', S', $Fr_{s''}$, and $Fr_{s'}$ have the same designation as in the preceding formulas.

The S-T segments (Leads I, II, CR_4, and CR_7) and the P-waves (Leads II, III, and CR_4) were corrected in the same manner as the T-waves.

The Changes in the Heart Rate during the Various Tests

The average changes in the heart rate as measured at 6—7 and 17—18 minutes' hypoxia appear from the tables given below.

Table 20. *Controls.*

		N	X	$s_{\bar{X}}$	|t|	P
Group I	Smokers	23	— 0.83 beats/min.	± 0.984	0.825	$0.4 < P < 0.5$
	Non-smokers	24	0.0 beats/min.	± 1.087	0	—
Group II		27	— 3.85 beats/min.	± 1.008	3.818	$P < 0.001$

Table 21. *Cigarette-tests.*

		N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
Group I	Smokers	26	9.88 beats/min.	± 1.774	5.462	$P < 0.001$
	Non-smokers	20	6.45 beats/min.	± 1.860	3.381	$0.001 < P < 0.01$

Table 22. *Cigar-tests.*

	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
Group I	19	8.05 beats/min.	± 1.763	4.445	$P < 0.001$
Group II	27	1.37 beats/min.	± 1.633	0.839	$0.4 < P < 0.5$

Table 23. *Nicotine-tests I.*

	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
Group I	23	6.78 beats/min.	± 1.906	3.479	$0.001 < P < 0.01$

Table 24. *Nicotine-tests II.*

	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
Group I	20	8.80 beats/min.	± 1.781	4.817	$P < 0.001$

Table 25. *The difference in heart rate between cigarette-tests and controls.*

		N	$\bar{Z}$	$s_{\bar{Z}}$	|t|	P
Group I	Smokers	22	11.59 beats/min.	± 1.777	6.372	$P < 0.001$
	Non-smokers	19	6.16 beats/min.	± 1.959	3.060	$0.001 < P < 0.01$

Table 26. *The difference in heart rate between cigar-tests and controls.*

	N	$\bar{Z}$	$s_{\bar{Z}}$	|t|	P
Group I	19	8.16 beats/min.	± 1.843	4.311	$P < 0.001$
Group II	27	5.22 beats/min.	± 1.714	3.046	$0.001 < P < 0.01$

Table 27. *The difference in heart rate between nicotine-tests I and controls.*

	N	$\bar{Z}$	$s_{\bar{Z}}$	|t|	P
Group I	23	7.96 beats/min.	± 2.071	3.758	$0.001 < P < 0.01$

Table 28. *The difference in heart rate between nicotine-tests II and controls.*

	N	$\bar{Z}$	$s_{\bar{Z}}$	|t|	P
Group I	18	7.78 beats/min.	± 1.893	3.994	$P < 0.001$

The tables thus demonstrate,

Controls. Group I, the heart rate showed no change. Group II, the heart rate decreased by 3 beats per minute.

Smoking-tests and nicotine-tests, Group I. There was a significant increase in heart rate.

Smoking-tests, Group II. There was no significant increase in heart rate.

In all smoking-tests (Group I and II) and nicotine-tests (Group I) there was a significant increase in heart rate compared with the controls.

There was no significant difference in heart rate between smokers and non-smokers, or between Group I and Group II.

The increase in heart rate during smoking is approximately the same whether under hypoxia or under ordinary circumstances.

The Changes in the T-Waves, S-T Segments, and P-Waves during the Various Tests

Group I

Controls — The time factor

The average change in the T-waves and S-T segments (measured in mm.) between the 6th and 17th minutes is shown in Tables 29—31.

Table 29. *Time factor concerning the T-waves. Smokers.*

Lead	N	X	$s_{\bar{X}}$
I	23	— 0.30 mm.	± 0.079
II	23	— 0.58 mm.	± 0.084
CR_2	23	— 0.99 mm.	± 0.174
CR_4	23	— 1.46 mm.	± 0.236
CR_7	23	— 0.63 mm.	± 0.101

Table 30. *Time factor concerning the T-waves. Non-smokers.*

Lead	N	X	$s_{\bar{X}}$
I	24	— 0.18 mm.	± 0.078
II	24	— 0.54 mm.	± 0.100
CR_2	23	— 1.35 mm.	± 0.247
CR_4	24	— 1.94 mm.	± 0.301
CR_7	23	— 0.42 mm.	± 0.098

Table 31. *Time factor concerning the S-T segments. Smokers and non-smokers.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$
I	47	— 0.09 mm.	± 0.026
II	47	— 0.13 mm.	± 0.040
CR_4	47	— 0.29 mm.	± 0.048
CR_7	46	— 0.09 mm.	± 0.040

Flattening of the T-waves and depression of the S-T segments thus occurred in all leads. The time factor is negative throughout.

Smoking-tests and nicotine-tests. Uncorrected values

The changes in the T-waves and S-T segments taking place after smoking or injection of nicotine are shown in Tables 32—38.

T-waves

Table 32. *Cigarette-tests. Smokers.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$
I	26	— 0.52 mm.	± 0.096
II	26	— 1.00 mm.	± 0.138
CR_2	26	— 1.70 mm.	± 0.234
CR_4	26	— 2.26 mm.	± 0.249
CR_7	26	— 1.15 mm.	± 0.170

Table 33. *Cigarette-tests. Non-smokers.*

Lead	N	X	$s_{\bar{X}}$
I	20	— 0.35 mm.	± 0.107
II	20	— 0.85 mm.	± 0.134
CR_2	18	— 1.26 mm.	± 0.205
CR_4	19	— 1.70 mm.	± 0.271
CR_7	18	— 0.52 mm.	± 0.156

Table 34. *Cigar-tests.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$
I	20	— 0.49 mm.	± 0.095
II	20	— 1.00 mm.	± 0.157
CR_2	20	— 1.70 mm.	± 0.280
CR_4	20	— 2.17 mm.	± 0.316
CR_7	20	— 0.88 mm.	± 0.139

Table 35. *Nicotine-tests I.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$
I	23	— 0.46 mm.	± 0.071
II	23	— 1.13 mm.	± 0.146
CR_2	23	— 1.60 mm.	± 0.198
CR_4	23	— 2.62 mm.	± 0.259
CR_7	23	— 1.02 mm.	± 0.169

Table 36. *Nicotine-tests II.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$
I	20	— 0.48 mm.	± 0.082
II	20	— 1.08 mm.	± 0.186
CR_2	19	— 1.57 mm.	± 0.263
CR_4	20	— 2.52 mm.	± 0.415
CR_7	19	— 1.28 mm.	± 0.236

S-T segments

Table 37. *Smoking-tests.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$
I	63	— 0.18 mm.	± 0.030
II	63	— 0.36 mm.	± 0.055
CR_4	61	— 0.61 mm.	± 0.071
CR_7	60	— 0.34 mm.	± 0.050

Table 38. *Nicotine-tests.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$
I	43	— 0.19 mm.	± 0.040
II	43	— 0.49 mm.	± 0.066
CR_4	43	— 0.86 mm.	± 0.095
CR_7	39	— 0.59 mm.	± 0.072

As can be seen, the flattening of the T-waves and the depression of the S-T segments was generally more marked in the smoking-tests and nicotine-tests than in the controls. (In the exercise tolerance tests the amplitudes of the T-waves decreased by an average of 2.79, 4.01, and 2.11 mm. in Leads CR_2, CR_4, and CR_7 (no table). S-T showed a depression of 0.84, 1.62, and 0.94 mm. in the same leads.)

The next point for consideration is whether there remains in the ECG any significant nicotine-effect after elimination of the heart-rate-effect.

The ECG Changes after Smoking and Injection of Nicotine after Correction According to Alternative I

The T-waves

Tables 39—43 demonstrate the effect of smoking and injection of nicotine on the T-waves after correction for the time factor and heart rate.

Table 39. *Cigarette-tests. Smokers.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	$\lvert t \rvert$	P
I	22	0.14 mm.	± 0.082	1.637	$0.1 < P < 0.2$
II	22	0.61 mm.	± 0.133	4.507	$P < 0.001$
CR_2	22	0.88 mm.	± 0.248	3.465	$0.001 < P < 0.01$
CR_4	22	1.59 mm.	± 0.387	4.010	$P < 0.001$
CR_7	22	0.92 mm.	± 0.191	4.699	$P < 0.001$

Table 40 *Cigarette-tests. Non-smokers.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	$\lvert t \rvert$	P
I	19	0.02 mm.	± 0.143	0.102	$0.9 < P < 1.0$
II	19	0.04 mm.	± 0.159	0.220	$0.8 < P < 0.9$
CR_2	17	0.65 mm.	± 0.394	1.594	$0.1 < P < 0.2$
CR_4	18	0.69 mm.	± 0.395	1.692	$0.1 < P < 0.2$
CR_7	17	0.36 mm.	± 0.243	1.448	$0.1 < P < 0.2$

Table 41. *Cigar-tests.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
I	19	0.05 mm.	± 0.116	0.420	$0.6 < P < 0.7$
II	19	0.20 mm.	± 0.208	0.939	$0.3 < P < 0.4$
CR_2	18	0.26 mm.	± 0.311	0.813	$0.4 < P < 0.5$
CR_4	19	0.96 mm.	± 0.322	2.909	$0.001 < P < 0.01$
CR_7	18	0.40 mm.	± 0.214	1.810	$0.05 < P < 0.1$

Table 42. *Nicotine-tests I.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
I	23	0.02 mm.	± 0.099	0.202	$0.8 < P < 0.9$
II	23	— 0.10 mm.	± 0.169	0.592	$0.5 < P < 0.6$
CR_2	23	0.14 mm.	± 0.258	0.543	$0.5 < P < 0.6$
CR_4	23	— 0.02 mm.	± 0.308	0.065	$0.9 < P < 1.0$
CR_7	23	0.26 mm.	± 0.194	1.340	$0.1 < P < 0.2$

Table 43. *Nicotine-tests II.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
I	18	0.09 mm.	± 0.138	0.634	$0.5 < P < 0.6$
II	18	0.28 mm.	± 0.183	1.489	$0.1 < P < 0.2$
CR_2	17	0.30 mm.	± 0.423	0.688	$0.5 < P < 0.6$
CR_4	18	0.43 mm.	± 0.457	0.915	$0.3 < P < 0.4$
CR_7	18	— 0.07 mm.	± 0.233	0.293	$0.7 < P < 0.8$

There is no flattening of the T-waves in any of the leads. In the cigarette-tests (smokers, Table 39) there is a significant increase in the amplitudes of the T-waves after correction.

The S-T segments

Tables 44—45 demonstrate the distance of the S-T segments in mm. from the P-Q level in smoking and nicotine-tests after correction.

Table 44. *Smoking-tests.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
I	60	0.01 mm.	± 0.039	0.256	$0.7 < P < 0.8$
II	60	— 0.01 mm.	± 0.058	0.172	$0.8 < P < 0.9$
CR_4	58	0.06 mm.	± 0.087	0.690	$0.4 < P < 0.5$
CR_7	56	— 0.05 mm.	± 0.060	0.833	$0.4 < P < 0.5$

Table 45. *Nicotine-tests.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
I	42	— 0.02 mm.	± 0.053	0.377	$0.7 < P < 0.8$
II	42	— 0.12 mm.	± 0.092	1.304	$0.1 < P < 0.2$
CR_4	42	— 0.25 mm.	± 0.100	2.500	$0.01 < P < 0.1$
CR_7	38	— 0.27 mm.	± 0.078	3.462	$0.001 < P < 0.01$

In the smoking-tests there is no significant change in the S-T segments after correction. (The figures for the cigarette and cigar-tests have been collected into a single table.) Nor in the nicotine-tests (I and II) is there any significant change in the S-T segments, except for Lead CR_7 in which a significant depression of 0.27 mm. has occurred.

The P-waves

Tables 46—47 demonstrate the changes in the amplitudes of the P-waves (Leads II, III, and CR_4) in cigarette and nicotine-tests after correction.

Table 46. *Cigarette-tests.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
II	39	0.22 mm.	± 0.063	3.492	$0.001 < P < 0.01$
III	40	0.23 mm.	± 0.099	2.323	$0.02 < P < 0.05$
CR_4	39	0.09 mm.	± 0.079	1.139	$0.2 < P < 0.3$

Table 47. *Nicotine-tests.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
II	41	0.10 mm.	± 0.057	1.754	$0.05 < P < 0.1$
III	40	0.09 mm.	± 0.064	1.406	$0.1 < P < 0.2$
CR_4	40	0.10 mm.	± 0.082	1.220	$0.2 < P < 0.3$

Only in the cigarette-tests (Lead II) is there any significant increase in the heights of the P-waves.

The ECG Changes after Smoking and Injection of Nicotine after Correction According to Alternative II

The T-waves

Tables 48—49 show the changes in the T-waves in the smoking-tests (cigarette and cigar-tests) and nicotine-tests (I and II) compared with corresponding changes in the exercise tolerance tests.

Table 48. *Smoking-tests.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
CR_2	63	1.35 mm.	± 0.149	9.060	$P < 0.001$
CR_4	64	2.26 mm.	± 0.180	12.556	$P < 0.001$
CR_7	63	1.00 mm.	± 0.086	11.628	$P < 0.001$

Table 49. *Nicotine-tests.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
CR_2	42	1.34 mm.	± 0.164	8.171	$P < 0.001$
CR_4	43	1.82 mm.	± 0.258	7.054	$P < 0.001$
CR_7	41	0.56 mm.	± 0.138	4.058	$P < 0.001$

The T-waves show thus considerably less marked flattening after smoking and nicotine than after physical work. The difference is highly significant.

The S-T segments

Tables 50 51 demonstrate the changes in the S-T segments in smoking-tests and nicotine-tests compared with corresponding changes in the exercise tolerance tests.

Table 50. *Smoking-tests.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
CR_4	63	0.42 mm.	± 0.077	5.455	$P < 0.001$
CR_7	62	0.60 mm.	± 0.048	12.500	$P < 0.001$

Table 51. *Nicotine-tests.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
CR_4	43	0.10 mm.	± 0.096	1.042	$0,3 < P < 0.4$
CR_7	39	0.34 mm.	± 0.071	4.789	$P < 0.001$

Like the T-waves, the S-T segments show a less marked depression in the smoking-tests than in the exercise tolerance tests. The difference is highly significant. In Lead CR_4 in the nicotine-tests, however, the difference is not significant.

Group II

Uncorrected Values of the T-Waves and S-T Segments

Tables 52—53 show the changes in the T-waves and S-T segments after cigar-smoking.

Table 52. *T-waves.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$
I	27	— 0.30 mm.	± 0.083
II	27	— 0.32 mm.	± 0.125
CR_2	26	— 1.23 mm.	± 0.244
CR_4	27	— 1.47 mm.	± 0.383
CR_7	27	— 0.59 mm.	± 0.203

Table 53. *S-T segments.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$
I	27	— 0.09 mm.	± 0.039
II	27	— 0.18 mm.	± 0.057
CR_4	26	— 0.44 mm.	± 0.122
CR_7	27	— 0.19 mm.	± 0.063

Flattening of the T-waves and depression of the S-T segments occurred in all leads.

The ECG Changes following Smoking, after Correction According to Alternative III

The changes in the T-waves and S-T segments in the smoking-tests after correction appear from Tables 54—55.

Table 54. *T-waves.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
I	27	— 0.15 mm.	± 0.048	3.125	$0.001 < P < 0.01$
II	27	+ 0.36 mm.	± 0.091	3.901	$P < 0.001$
CR_2	26	— 0.45 mm.	± 0.222	2.045	$0.05 < P < 0.1$
CR_4	27	— 0.11 mm.	± 0.297	0.381	$0.7 < P < 0.8$
CR_7	27	— 0.03 mm.	± 0.173	0.173	$0.8 < P < 0.9$

Table 55. *S-T segments.*

Lead	N	$\bar{X}$	$s_{\bar{X}}$	|t|	P
I	27	— 0.05 mm.	± 0.037	1.351	$0.1 < P < 0.2$
II	27	— 0.10 mm.	± 0.051	1.961	$0.05 < P < 0.1$
CR_4	27	— 0.10 mm.	± 0.114	0.877	$0.3 < P < 0.4$
CR_7	26	— 0.05 mm.	± 0.050	1.000	$0.3 < P < 0.4$

After correction the T-waves show significant flattening in Lead I and a highly significant increase in Lead II. The S-T segments show no significant change after correction.

It thus appears from the above tables that on smoking (Groups I and II) or intravenous injection of nicotine (Group I) during hypoxia a significant increase in heart rate generally develops together with simultaneous flattening of the T-waves and depression of the S-T segments. The P-waves, however, increase in height under the same conditions. The regression coefficients of the P-waves in Leads II, III, and CR_4 in the cigarette-tests were calculated to + 0.026, + 0.012, and + 0.032 respectively.

By means of the statistical analyses we may now answer the question of whether nicotine has any further effect on the electrocardiogram after elimination of its effect of quickening the heart rate.

In *Group I* there is no significant flattening of the T-waves after correction of the ECG changes for heart rate, and a significant increase in the amplitude

of the T-waves was actually noted in the cigarette-tests (smokers, Table 39) in four of five leads after correction. This may have been due to the fact that smokers react differently from non-smokers to cigarette-smoking. In Lead CR_7 (Table 45) there is a significant depression of the S-T segment of 0.3 mm. Thus in only one of the eight leads (Tables 44—45) is there a slight depression of the S-T segment after correction for the influence of heart rate.

The exercise tolerance tests show that during hypoxia the T-waves and S-T segments are on average less influenced by smoking and nicotine than by physical work.

In *Group II* after correction there is a significant flattening of the T-waves by 0.15 mm. in Lead I and a significant increase by 0.36 mm. in Lead II, which changes do not allow of any definite conclusions. The S-T segments show no significant changes after correction for heart rate. (The T-waves in the smoking-tests have subsequently been corrected also by Alternative I, with approximately the same result as with Alternative III.)

The T-waves may also be influenced by changes in the position of the heart. The literature on this subject has been summarized by Björkman (1951). The position of the heart is constantly changing with changes in the diaphragm's position during hypoxic respiration. On inspiration the R and T-waves become smaller in Lead I and increase in height in Lead III; and on expiration they increase in Lead I and decrease in Lead III (Leimdorfer, 1948). During the hypoxia test significant hyperventilation most frequently occurs which, however, becomes constant after the first 5 minutes in both smoking-tests and controls. It may therefore be assumed that the position of the heart varies within the same limits from the 6th minute of the test onwards. Any variations in the amplitude of the T-waves due to respiratory movements should thus be approximately equal in the various experiments. In some of nicotine-tests II (3 mg. of nicotine), however, hyperventilation increased further during the tests, as a result of the stimulant effect of nicotine on the respiration (Chapter VIII). The position of the electrical axis (angle α) was examined in five cases before and after injection of nicotine: in four of the five cases angle α (the mean between inspiration and expiration) remained unchanged; in the fifth case, in which injection of nicotine produced severe hyperventilation, angle α was $+67^\circ$ before and $+76^\circ$ after the injection (mean values).

Nicotine can also cause hypopotassaemia (Chapter XI), which might have the effect of flattening the T-waves. The serum potassium was determined in seven cases immediately before and after intravenous injection of 2—3 mg. of nicotine. No significant change in this value was noted.

The changes in the position of the heart and in the electrolyte balance of the blood (serum potassium) occurring during these experiments are probably so slight that they may be disregarded.

Summary

Smoking or injection of nicotine during hypoxia generally results in quickening of the heart rate and simultaneous flattening of the T-waves and depression of the S-T segments. These ECG changes are partly due to the hypoxia in itself (the 'time factor'), and partly to the nicotine. After adjusting the amplitudes of the T-waves and the S-T segments regarding the time factor and changes in heart rate — according to three different alternatives all with the same tendency — there remains little or no effect of nicotine on the ECG. *The ECG changes provoked by smoking or injection of nicotine (in the doses employed here) during hypoxia are thus chiefly due to the simultaneous increase in heart rate.*

Physical work during hypoxia produces a more marked flattening of the T-waves and depression of the S-T segments than does smoking or nicotine under the same conditions.

CHAPTER XI

The Electrocardiogram in Acute Nicotine Poisoning

In the preceding chapters the effect of relatively small amounts of nicotine on the electrocardiogram has been discussed. It may be asked in what way large and toxic amounts of nicotine influence the ECG, and whether they produce pathological ECG changes. In a previous paper the effect of nicotine (0.97, 3.25, 6.50, 9.75, 14.62, and 19.50 mg. alkaloid/kg.) on the electrocardiogram in rabbits was reported (von Ahn, 1952). The lowest dose of nicotine which had any significant effect on the ECG was 3.25 mg. per kg. body-weight; the lethal dose of nicotine in rabbits was found to be 6.50 —19.50 mg. per kg. body-weight. Injection of *non-lethal doses of nicotine* produced ECG changes as follows:

1. The heart rate appeared to be the most sensitive indicator of the influence of nicotine. In significant cases a rapidly commencing bradycardia of 10 to 20 minutes' duration occurred and without subsequent increase in frequency.

2. Arrhythmia of irregular or sinus type appeared simultaneously with the bradycardia.

3. Auriculo-ventricular nodal rhythm was very rare.

4. Extrasystoles, usually of supra-ventricular type, were also rare.

5. Sino-auricular block occurred quite frequently.

6. First-degree auriculo-ventricular block was observed in 5 of 24 experiments. Higher degrees of A-V block did not occur.

7. Neither auricular flutter nor auricular fibrillation was recorded in any case.

8. The T-waves did not show significant changes in any case. (The T-waves in rabbits show considerable spontaneous variation, and must therefore be judged with great caution.)

Lethal doses of nicotine caused:

9. First-degree auriculo-ventricular block with great prolongation of the P-R interval, disturbances of intraventricular conduction, elevated onset of

R-T in Leads I and II, in one case depressed R-T, characteristic high, sharp T-waves, and ventricular fibrillation.

Thus only lethal doses of nicotine influence significantly the RS-T segment and the T-waves. Immediately before death abnormally high, sharp T-waves of the type 'Erstickungs-T' described in asphyxia in dogs (Miki, 1922; Dietrich and Schimert, 1933) occurred in 4 of the 5 animals in which lethal doses were administered. The cause of death in acute nicotine poisoning is considered to be asphyxia due to peripheral paralysis or fixation of the respiratory muscles (Franke and Thomas, 1936). It is probable that the high, sharp T-waves in the rabbit ECGs are also a sign of severe myocardial anoxia.

The ECG changes *in acute nicotine poisoning in man* are of special interest in this connection. The literature on this subject is reviewed in a previous paper (von Ahn, 1952) from which it can be seen that electrocardiograms have been recorded only in a few such cases. Laessing (1938) found in a case of severe acute nicotine poisoning in a man aged 25 years bradycardia, arrhythmia, low and isoelectric T-waves, and depression of the S-T segment. He considered these ECG changes to be signs of myocardial damage. This view may however be questioned: it seems that Laessing has overlooked the fact that nicotine can provoke functional ECG changes viz. by causing disturbances in the electrolyte balance, in particular hypopotassaemia. In one case of acute nicotine poisoning the value of the serum-potassium decreased to 10.6 mg% (von Ahn, 1953). This in itself would be enough to produce transient pathological ECG changes, which thus need not be interpreted as signs of a myocardial lesion or coronary insufficiency.

Sinus bradycardia and arrhythmias of the extrasystole type have been reported in cases of acute nicotine poisoning. One case of sino-auricular block in a child (Gyllenswärd and Nordbring, 1953) and two of paroxysmal auricular fibrillation in adults (von Ahn, 1952, 1953) have also been reported In these three cases the patients recovered relatively quickly without after-effects. In one of the cases of fibrillation (1952) the heart rate was 124 beats per minute with conspicuously low T-waves which may have been at least partly due to the increased heart rate. The second case (1953) showed a heart rate of 55 beats per minute, unusually high T-waves, and depressed S-T in all leads.

The ECG changes in acute nicotine poisoning are probably caused by several different factors. Nicotine in toxic doses may affect the heart both directly and indirectly in the following ways:

(1) by powerfully stimulating the vagus via the vagal centre, which predisposes to auricular fibrillation, and possibly resulting in coronary ?spasm.

(2) by provoking arrhythmia via the hypothalamus (Dikshit, 1934);

(3) by humoral agents (adrenaline and posterior pituitary hormone), which accentuate any possible myocardial hypoxia (see point 1);

(4) by *disturbing the electrolyte balance (hypopotassaemia);*

(5) by a possible toxic effect on the myocardium.

The cases of acute nicotine poisoning which have come under clinical observation have generally been of short duration. In the few cases in which an ECG has been recorded, any changes have lasted only a few hours and have obviously been functional in character. There is nothing to indicate that nicotine in large doses could cause acute myocardial damage (heart infarction): this however has been reported after injection of pitressin in man (see Chapter IV).

The ECG changes observed in acute nicotine poisoning in man may to a great extent be ascribed to disturbances in the electrolyte balance (hypopotassaemia).

CHAPTER XII

Tobacco Angina

It is common knowledge that tobacco-smoking can provoke chest pains in both healthy persons and cardiac patients. In the literature these pains go under the name of 'Tobacco Angina' (see Chapter I). Cases of 'Tobacco Angina' have been described by Huchard (1899), Willson (1915), Allbutt (1915), Fiessinger (1919), Külbs (1924), Gallavardin (1925), Rolleston (1926), Moschcowitz (1928), Schlayer (1928), Cornwall (1934), and Unverricht (1941). Allbutt and Moschcowitz have given a particularly graphic account of this syndrome. Moschcowitz pointed out that there are two distinct types of 'tobacco heart' that without signs of coronary disease, and that with. From my own observations it seems that two distinct types of 'tobacco angina' can be distinguished, viz. *true tobacco angina* (the *tobacco angina* of this study) and *angina pectoris precipitated by tobacco-smoking*. In the literature these two types of tobacco angina are seldom distinguished, although they are essentially different both in character and prognosis.

Tobacco angina is relatively common in heavy smokers. It affects not infrequently clinically healthy persons, sometimes young people, and may be defined as a pain resembling that of angina pectoris but exclusively precipitated by tobacco-smoking. The pains develop some time after the smoking, often only after one or several hours. Tobacco angina is not as a rule aggravated by physical exertion, and in most cases in which I have tried nitroglycerine this has been without effect. Unlike angina pectoris, the pains are not usually of paroxysmal type, but are continuous and occasionally intense. Tobacco angina may therefore simulate heart infarction. The pains characteristically disappear completely on giving up smoking, but may continue long afterwards — for days, weeks, or even years (Allbutt; Moschcowitz; Connamacher). Gallavardin states that tobacco angina can sometimes be preceded by an aura of abdominal or cerebral type. The origin of the pain is obscure. Huchard in his time considered it to be due to coronary spasm, and many authors after him have been of the same opinion (Chapter I). There are however as yet no observations to support the theory that

tobacco angina is due to myocardial anoxia. It is very improbable that continuous chest pains with a duration of say several months could be due to coronary insufficiency, especially as many of these cases are young persons with otherwise clinically healthy hearts. I have performed smoking-tests in some typical cases of tobacco angina without finding any pathological ECG changes. My own observations suggest that there is a great similarity between tobacco angina and the functional cardiac pain of neurocirculatory asthenia. It has also been questioned whether tobacco angina is a kind of neuralgia due to toxic stimulation of the cardiac ganglia (Willson). According to Moschcowitz this syndrome resembles true neuralgia.

Two cases of typical tobacco angina will be described. The subjects are both doctors, able to give an accurate description of their symptoms.

Case 1. Radiologist, cigarette smoker since the age of 19. His cigarette consumption gradually increased to a maximum of 20—25 cigarettes per day. He became troubled by degrees with precordial pains after increasing his tobacco consumption, the pains usually coming on after the third or fourth cigarette in the 'chain'. The pains occurred both at rest and in connection with physical exertion. They came on insidiously, almost imperceptibly, and subsided gradually after one or several hours. After 16 years' smoking a dramatic situation occurred, which is best related in own words. 'At the age of 35, I had smoked unusually heavily during one day, and spent the evening at a restaurant smoking intensively until midnight. I also drank a certain amount of spirits during the evening, probably 100—150 cc. Later that night I had a very severe attack of precordial pains; the heart felt as though gripped in a vice from behind, I was apprehensive and uneasy, and came out in a cold sweat. The pain seemed to go on for ages, but it cannot have lasted more than two hours in reality'. He never smoked after this attack and has since had only insignificant cardiac symptoms. His physical efficiency has increased considerably.

Case 2. Radiologist, cigarette-smoker. His tobacco consumption increased gradually, and sometimes amounted to 50—60 cigarettes a day — an impressive amount. At the age of 34, after about 16 years' cigarette-smoking, he became troubled with pains in the region of the heart. The pains came on suddenly and were quite severe, lasting several minutes, and did not radiate. They generally took place in the middle of the day, and never at night, always occurring at rest and never on physical exertion. During the next few years after he had stopped smoking he was still troubled with pains; these decreased gradually in frequency, duration, and intensity, finally to cease altogether.

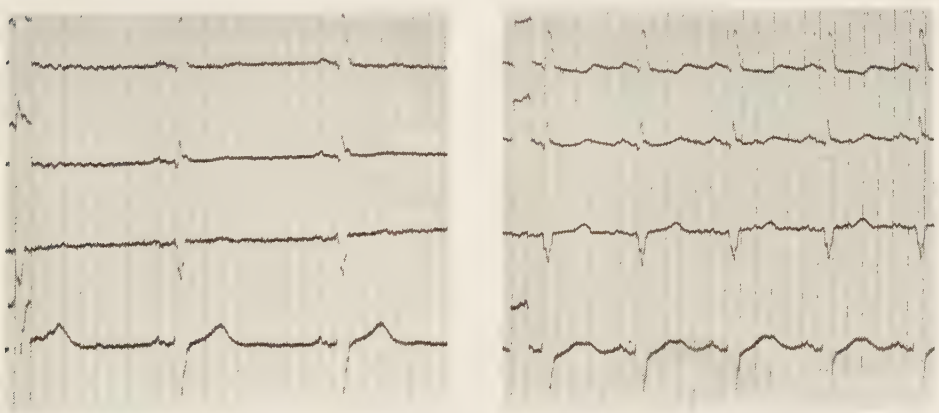
These two cases illustrate true tobacco angina with good prognosis in persons with clinically healthy hearts.

As mentioned above (Chapter III), both tobacco-smoking and injection of nicotine can precipitate angina pectoris with simultaneous pathological ECG changes in patients with coronary disease. Only a few such cases have previously been described in the literature — Wilson and Johnston (1939, 1941), two cases; Harkavy (1946), one case; Bryant and Wood (1947), two cases; Boyle, Wegria, Cathcart, Nickerson, and Levy (1947), two cases (after injection of nicotine); Arai, Pordy, Chesky, and Master (1951), one case; and Moschini-Antinori and Solinas (1951), one case. Cases of angina

pectoris precipitated by tobacco-smoking have also been described by Ralli and Oppenheimer (1928) and by Pickering and Sanderson (1945), but these authors did not record electrocardiograms. Birk and Huber (1939) described three cases of angina pectoris with ECG changes which they ascribed to tobacco-smoking; to judge from the histories, however, none of the 'pathological' ECG changes occurred in immediate association with smoking. In one case (Case 3) smoking provoked tachycardia and a simultaneous flattening of the T-waves in Lead II, which was probably only a 'physiological' sequel of the increased heart rate.

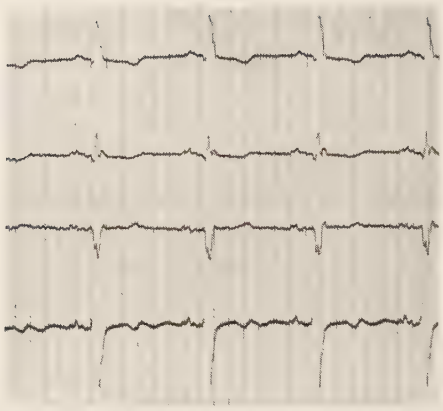
I have found three cases of coronary disease in which smoking provoked typical anginal pains with simultaneous ECG changes. The first case has already been published in the American Heart Journal (von Ahn and Göhle, 1949), but for the sake of completeness I will describe it briefly here. The second case was sent for examination to the Medical Department, Academic Hospital, Uppsala through the kindness of Dr. Herbert Bjerlöf, Stockholm. The third case is one of our own patients at the Academic Hospital, Uppsala.

Case 3. A 57-year-old typhographer with an 8-year history of typical angina pectoris. Had smoked since the age of 14 a maximum of 30 cigarettes per day. During his last years his tolerance of tobacco had decreased successively to the extent that an attack was promptly precipitated by smoking. Several hours after the smoking of about half a cigarette minor degrees of physical exertion would precipitate severe angina pectoris; but if he had not smoked recently he could go far long walks without appreciable disability. One or two puffs at a cigarette produced a typical anginal attack with rapid increase in pulse-rate and serious but reversible ECG changes (ECG nos. 38—40).



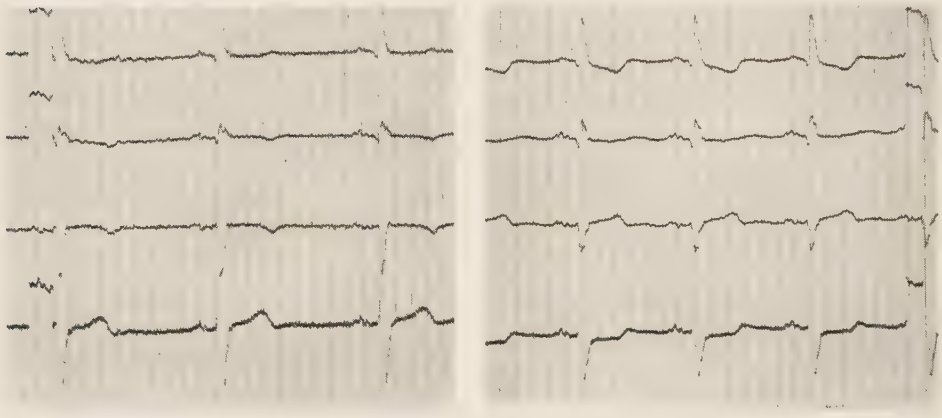
ECG no. 38. Case 3. ECG during rest and abstinence.

ECG no. 39. ECG after 45 seconds' smoking: real pains.



ECG no. 40. ECG after 6 minutes' smoking: the pains begin to subside.

Even moderate meals provoked severe anginal attacks (ECG nos. 41—42).



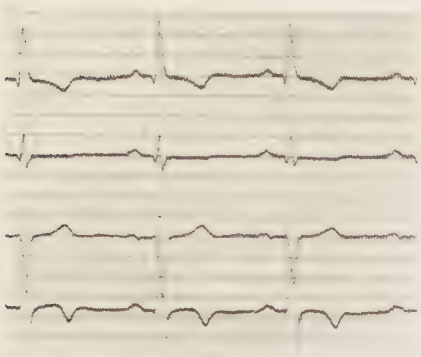
ECG no. 41. ECG before meal.

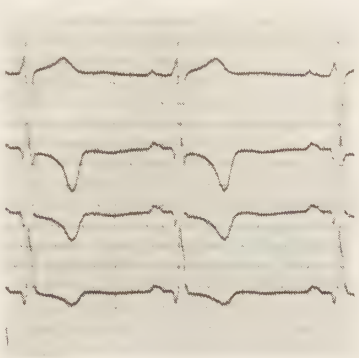
ECG no. 42. ECG 6 minutes after the meal: bad pains.

Case 4. (Record no. 236/53). Caretaker, aged 60 years, smoker since the age of 18. For the last 8 years he has suffered from oppressive sub-sternal pains, radiating towards both shoulders and down to the hands, and provoked by physical exertion.

Four years ago he noticed that the smoking of one cigarette would considerably impair his physical efficiency. His susceptibility to tobacco has since increased successively; the smoking of one cigarette together with moderate physical exertion, will now precipitate severe anginal pains; and a meal combined with smoking will also produce severe physical disablement, particularly if spirits are taken. Condition on admission January 14th, 1953:

Build pyknic. Pulse 72, blood-pressure 175/100—150/110 mm. Hg. Heart sounds diminished, clear, regular. Chest normal. Abdomen normal. Tendon reflexes normal. Blood and urine normal. X-ray of the heart showed heart volume 600 ml. per m^2. body surface, left ventricle enlarged. ECG at rest, see below (ECG nos. 43—44).

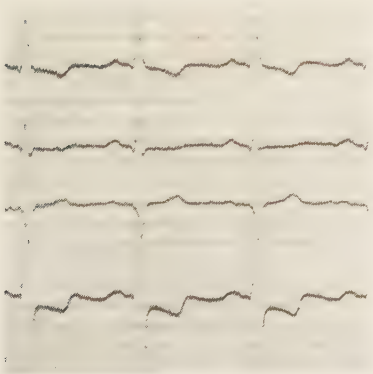


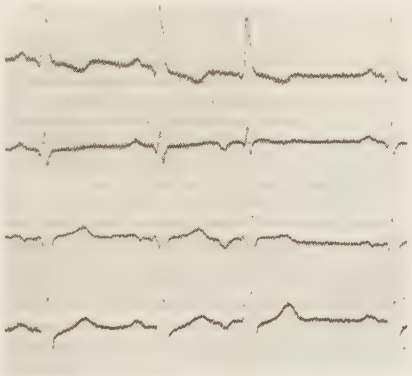


ECG no. 43. Case 4. ECG in a fasting state during rest and before smoking. Leads I, II, III and CR_4.

ECG no. 44. Chest Leads CR_2, CR_5, CR_6, CR_7.

The patient underwent smoking-tests during which electrocardiograms were recorded. After the smoking of one cigarette in 8 minutes he developed typical anginal pains and his pathological ECG changes became accentuated, indicating increased myocardial anoxia. The course of events during the smoking-test is illustrated by electrocardiograms nos. 45—46.



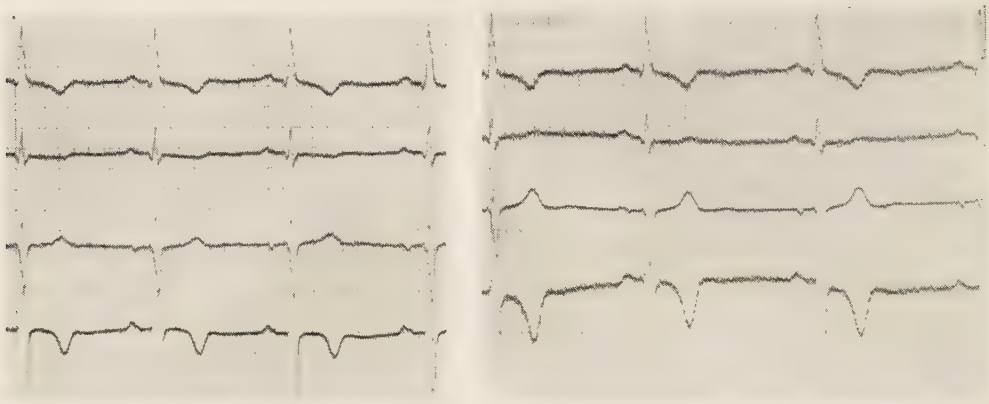


ECG no. 45. ECG 10 minutes after the smoking of one cigarette in 8 minutes, and after 7 drops of nitroglycerine. Anginal pains. Heart rate 85 beats per minute. S-T depressed in Lead CR_4.

ECG no. 46. ECG 9 minutes after nitroglycerine. No pains. Heart rate 80 beats per minute. S-T less markedly depressed in Lead CR_4.
A supraventricular extrasystole.

During the smoking-test the blood-pressure increased from 150/110 mm. to a maximum of 186/134 mm. Hg. after 7 minutes' smoking. After 13 minutes' cigarette-smoking the patient complained of severe anginal pains, and smoking was stopped. The pains subsided completely after 7 drops of nitroglycerine by mouth. Simultaneously with the pains a considerable depression of S-T in Lead CR_4 occurred; this gradually returned to the initial level after nitroglycerine.

As the patient also complained of anginal attacks in connection with meals, electrocardiograms were recorded before and after a meal (ECG nos. 47—48).



ECG no. 47. ECG in a fasting state. Heart rate 65 beats per minute.

ECG no. 48. ECG 2 minutes after meal with porridge, milk and two sandwiches. Slight substernal pains. Heart rate 55 beats per minute. T in Lead CR_4 more deeply negative.

A meal thus accentuates substantially the patient's coronary insufficiency. These investigations make it clear that his physical efficiency is greatly reduced by smoking + a meal.

Case 5. (Record no. 33/53). Former railway clerk, aged 62 years, smoker since the age of 16. Has had at least three infarcts during the years 1942—48. Before the first he could smoke without disability. When he came home from hospital after the first attack he started to smoke again, but with precordial pains as result. These increased gradually in intensity, and after 2—3 months the pains were so severe that he had to stop smoking and has not smoked since then. For the past 3—4 years he has had considerable epigastric pain which comes on both after minor degrees of physical exertion and after light meals. Since recently even a glass of water will precipitate the pains.

On examination on April 4th 1953 the pulse-rate was about 60 per minute and the blood-pressure 115/80 mm. Hg. The heart was considerably enlarged, and the rhythm irregular. ECG showed auricular fibrillation + isolated ventricular extrasystoles (ECG no. 49). X-ray showed the heart to be considerably enlarged (volume 1340 ml. $m.^2$ body surface).

A light meal produced moderate epigastric pain (Fig. 1.) and bradycardia. ECG after the meal showed slow auricular fibrillation and coupled beats.

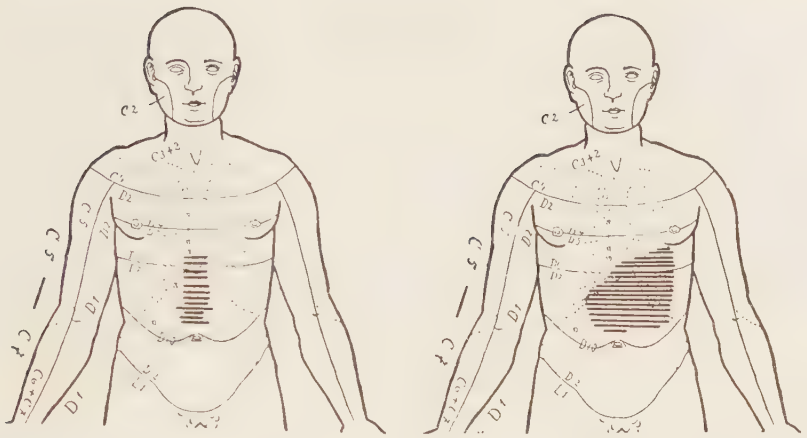
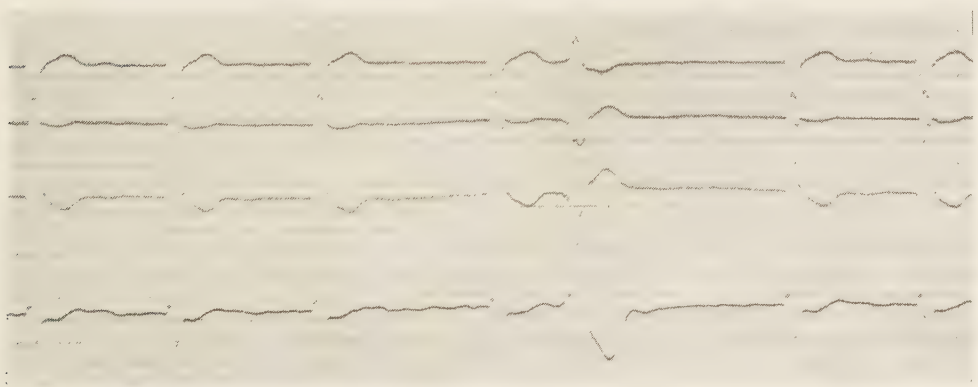


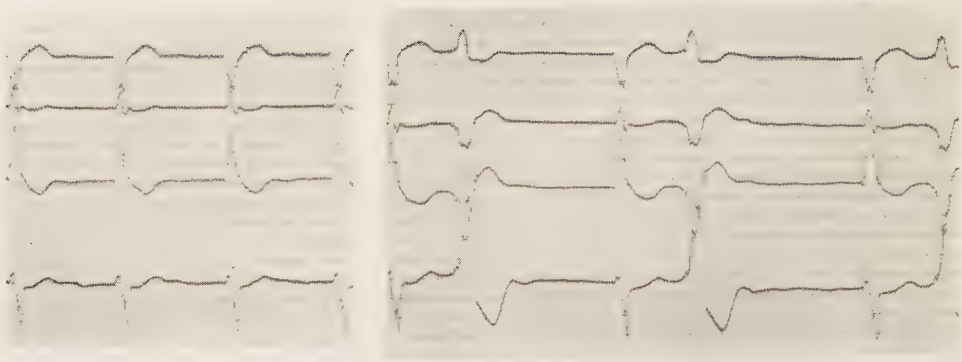
Figure nos. 1 and 2.

Fig. 1 demonstrates the location of the pains in the abdomen after a meal and Fig. 2 after the smoking of one cigarette with inhalation.

After the smoking of one cigarette in a fasting state the patient developed considerably more severe and widely-spread abdominal pains than those occurring after a meal (Fig. 2.). During the smoking-test the heart rate at first increased from c. 60 beats per minute at rest to c. 85 after 3 minutes' smoking (ECG no. 50). After 10 minutes' smoking he developed slight toxic symptoms, and the heart rate decreased to c. 40 beats per minute. The abdominal pains subsided quickly on administration of nitroglycerine. After the end of the smoking-test the ECG had the same pattern as after the meal — slow auricular fibrillation + coupled beats. The ECG pattern (ECG no. 51) is similar to that seen in digitalis poisoning.



ECG no. 49. ECG during rest and abstinence, Auricular fibrillation + isolated ventricular extrasystoles. Heart rate c. 60 beats per minute. Blood-pressure 130/78 mm. Hg.



ECG no. 50. ECG after 3 minutes' cigarette-smoking. No extrasystoles. Heart rate c. 85 beats per minute. Blood-pressure 114/96 mm. Hg.

ECG no. 51. ECG after 10 minutes' smoking. Slow auricular fibrillation + coupled beats. Heart rate c. 40 beats per minute. Moderate abdominal pains. Blood-pressure 130/80 mm. Hg.

These cases prove that tobacco-smoking can indeed precipitate acute coronary insufficiency. The explanation is not clear. Wilson and Johnston are of the opinion that smoking can precipitate angina pectoris by increasing the work of the heart or by inducing coronary spasm. In Case 3 a rapid increase in heart rate by 40 beats per minute occurred during the smoking-test, and in Case 4 a considerable increase in blood-pressure (and thus increased strain on the heart) took place. This may be a satisfactory explanation. Even at rest, both patients had a greatly diminished coronary reserve; this clearly was further reduced when additional strain was put on the heart, so that the latent coronary insufficiency became manifest. Furthermore, increase in blood-pressure may, via the carotid sinus, reflexly produce coronary constriction and thus also angina pectoris. In Case 5 the increase in heart rate was not so marked and the diastolic blood-pressure showed only a transient increase by 18 mm. Hg. It is possible that coronary spasm induced by tobacco was an essential contributory cause of the anginal pains in all the three cases. As already mentioned (see Chapters III and IV), it is rare for tobacco-smoking directly to precipitate angina pectoris in cardiac patients. Obviously this only occurs under special conditions. It has been alleged that tobacco-smoking over many years might result in allergy with angina pectoris or tachycardia among the sequelae (Harkavy, 1938, 1946; Unverricht, 1941; Knight, 1950). According to Harkavy (1946) the shock organ in such allergic individuals is represented by the coronary vessels and the myocardium. It is possible that there was a cardiovascular susceptibility to tobacco in the above-described cases, the coronary vessels being affected and spasm

resulting. The existence of coronary spasm was long held to be an unproved hypothesis (Echave, 1952), but lately it has been confirmed by Spritzler et al. (1952) in experiments on dogs.

Angina pectoris precipitated by tobacco-smoking only occurs in patients with coronary disease. This syndrome is quite different from and has a much more severe prognosis than *true tobacco angina*, which is relatively common, and can of course also occur in cardiac patients. Tobacco angina can then be difficult to distinguish from angina pectoris. This confusion is surely an essential reason, why tobacco-smoking used to be considered to play an important part in the aetiology of angina pectoris.

Summary

Tobacco-smoking can provoke two distinct types of pain:

1. *Tobacco Angina*, which is relatively common in heavy smokers, both healthy subjects and cardiac patients. The pains do not develop in immediate association with smoking, but as a rule only after one or several hours. They often are of long duration. The aetiology of the pain is unknown, but there is no evidence to show that it is of coronary origin.

2. *Angina pectoris precipitated by tobacco-smoking*. This rare syndrome only occurs in patients with coronary disease, and it always develops in immediate relation to tobacco-smoking. The pains are clearly of coronary origin, and are associated with pathological ECG changes.

Summary and Results

The aim of this study has been to investigate the immediate effect of tobacco-smoking and injection of nicotine on the electrocardiogram, especially during induced hypoxia.

A brief review of the literature on the effect of tobacco on the cardiovascular system is given in *Chapter I*. Many authors have alleged that excessive tobacco-smoking may exert a deleterious effect on the heart partly by provoking coronary spasm and precipitating angina pectoris, and partly by predisposing to arteriosclerosis. This view has been modified considerably in recent years, but opinions on the possible deleterious effects of tobacco-smoking on the heart are still conflicting.

A survey of the pharmacology of smoking and an account of animal experiments done to investigate the effect of nicotine on the coronary circulation are given in *Chapter II*. Nicotine may exert inter alia an indirect effect on the coronary circulation via humoral agents such as adrenaline and posterior pituitary hormone (pitressin). According to Burn et al., tobacco-smoking may produce coronary constriction by liberation of posterior pituitary hormone. A brief review of the literature on the influence of smoking on the peripheral circulation in man is also given.

Previous investigations into the influence of tobacco-smoking on the electrocardiogram are reported in *Chapter III*. The constant electrocardiographic findings have been an increase in heart rate with simultaneous slight flattening of the T-waves. Some authors have considered these ECG changes to be of coronary origin, whereas others have considered them to be due to increased sympathetic tone. In patients with coronary disease, however, tobacco-smoking can in rare cases precipitate angina pectoris with transient pathological ECG changes.

Observations advanced in support of the possible deleterious influence of tobacco on the action of the heart are discussed in *Chapter IV*.

Experiments on dogs have shown that an artificially infarcted heart is much more susceptible to tobacco-smoke and nicotine than a normal one (*Chapter V*). The object was thus to establish whether in man, too, nicotine exerts a more marked effect on the heart during induced hypoxia than under ordinary circumstances. If this were correct heavy tobacco-smoking

or injection of nicotine during hypoxia might be expected to provoke pathological ECG changes.

Chapter VI contains an account of the series and the experimental methods.

The changes in oxygen saturation and blood-pressure in the various tests are described in *Chapter VII*. The arterial oxygen saturation decreased by 2—3 % during both smoking-tests and control-tests, but increased by c. 3 % in the nicotine-tests compared with the controls. There was a significant increase in systolic blood-pressure by 6—10 mm. Hg. in the smoking tests (Group I and II), and a probably significant increase in diastolic pressure (Group I) by c. 3 mm. Hg. compared with the controls. In the nicotine-tests (Group I) there was no significant change in systolic and diastolic blood-pressure compared with the controls.

Some of the electrocardiographic findings are shown in *Chapter VIII*. After 5—6 minutes' hypoxia the oxygen saturation and heart rate have become stabilized, but in spite of this a spontaneous flattening of the T-waves (here called the time factor) is seen in the controls. After smoking and nicotine an increase in heart rate, slight depression of the S-T segments, and further flattening of the T-waves develop. Smoking or injection of nicotine under hypoxia provoke essentially the same ECG changes. Dihydroergotamine impedes the effect of nicotine on the ECG.

The aetiology of the ECG changes is discussed in *Chapter IX*, in which comparative hypoxia experiments with nicotine, adrenaline, atropine, and physical work are described. Adrenaline causes an abrupt flattening of the T-waves; nicotine, atropine, and physical work result in a moderate flattening of the T-waves simultaneously with increase in heart rate. In certain cases heavy smoking and injection of nicotine can flatten the T-waves without simultaneously increasing the heart rate. Nicotine has in these cases an effect on the ECG similar to that of adrenaline. During hypoxia the T-waves are less markedly flattened by smoking or injection of nicotine than by physical work.

The statistical analysis of the electrocardiographic findings is reported in *Chapter X*. The heart rate increased by an average of 5—11 beats per minute in the smoking-tests and nicotine-tests compared with the controls. The T-waves, S-T segments, and P-waves were corrected for the influence of heart rate according to three different alternatives, the same tendency being found in each case. After correction for heart rate there was no flattening of the T-waves (except in Lead I, Group II) or depression of the S-T segments (except in one of eight leads, Group I). These findings all support the assertion that *the effect of nicotine on the ECG* (in the doses employed here) *is chiefly due to the increased heart rate.*

The influence of toxic doses of nicotine on the ECG is described in *Chapter XI*. The results of the author's own previous experiments on rabbits are

reviewed. An account is also given of the electrocardiogram in acute nicotine poisoning in man.

Tobacco-smoking can provoke two distinct types of pain, (1) Tobacco Angina and (2) Angina pectoris precipitated by tobacco-smoking *(Chapter XII)*. Three cases are described, in which angina pectoris with transient pathological ECG changes was provoked by tobacco-smoking in patients with severe coronary disease.

Conclusions

1. Tobacco-smoking or injection of nicotine during hypoxia results in increase in heart rate, increase in the amplitudes of the P-waves, flattening of the T-waves, and slight depression of the S-T segments.

2. These ECG changes are due chiefly to increased sympathetic tone. This is supported by following facts.

(a) Dihydroergotamine impedes the effect of nicotine on the electrocardiogram; on the other hand, heavy smoking can change a vagotonic ECG in a sympatheticotonic direction.

(b) Atropine may lead to approximately the same degree of flattening of the T-waves as nicotine.

(c) There is practically no flattening of T-waves or depression of S-T segments after elimination of the heart-rate-effect due to smoking or injection of nicotine.

3. Physical work during hypoxia leads to more marked flattening of the T-waves and depression of the S-T segments than does nicotine under the same conditions.

4. In certain cases heavy smoking or injection of nicotine results in flattening of the T-waves without simultaneously incurring increase in heart rate. This is probably due to increased adrenal secretion.

5. It is very unlikely that the ECG changes provoked by smoking or injection of nicotine during hypoxia in persons with clinically healthy hearts are of coronary origin.

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